GENETICS
AND
DISEASE

GENETICS AND DISEASE

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EJNAR MUNKSGAARD COPENHAGEN 1951

Translated from the Danish by

ELISABETH AAGESEN

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1951

Revised by

James Andrews, M.B., B.S., London

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Vald. Pedersens Bogtrykkeri

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PART II MEDICAL GENETICS

PART III NORMAL HEREDITARY FACTORS IN MAN

CHAPTER I

THE RISE OF HUMAN GENETICS

From early times people have realized that parents and their offspring are alike in some ways, unlike in others; that relatives present similarities and differences, partly on account of their inherited nature and partly owing to environmental influences

Since classical times it has been a well-known fact that many defects and diseases run in families, frequently causing destruction of the affected lineage.

The Ancient Greeks were interested in almost the same genetic problems as modern workers, though their empirical material was smaller. The naturalists and philosophers of those days knew practically as much about genetics as nineteenth century scientists

Further progress could not be made within this field till the discovery of the fundamental genetic laws In 1865 Gregor Mendel established the main features of inheritance through his simple experiments with garden-peas in the convent garden at Brno Until then vague ideas had been entertained that characteristic properties of two parents would be blended in the offspring Mendel observed, however, how the hereditary factors, each of which is immutable, are separated unblended at the fertilisation, to be united again in new combinations in the offspring This double-action of inheritance explains both the striking resemblance of, and the many points of dissimilarity between parents and offspring

Mendel's discovery remained unknown to the world for many years. The conditions for an understanding of it were not yet present.

Ten years after the publication of Mendel's work a fusion was demonstrated to take place at the fertilisation between the nuclei of the 2 sex-cells That same year the chromosomes were discovered After another ten years, in 1885 the hereditary traits were found to be localized in the nucleus of the cell At the same time it was realized how, during cell division, the chromosomes split longitudinally in 2 halves, how they wander towards the poles at the vegetative divisions, and are reduced to half their original number when the mature sex-cell develops

These observations provided a basis for an understanding of Mendel's laws, which in 1900 were rediscovered almost simultaneously by de Vries in

PART V. GENETIC HYGIENE

the slightest changes and the finest shades of differences in the appearances of one generation from the next. Furthermore, like Mendel in his well-known experiments, they directed their attention towards the numerical distribution of the different types in the descendants.

These comprehensive crossing experiments, combined with analyses of the offspring, revealed that the genes carried in the same chromosome, cannot be separated freely, but are *linked*, although *crossing-over* from one partner to the other in a chromosome pair may occur. Through crossing-over experiments it was possible to demonstrate how the genes lie linearly arranged, like beads on a string, along the chromosomes, and further to determine the sites of a great number of genes in the chromosomes of the fruit fly. Similar experiments have been made with other plant and animal species, and we know the sites of several genes, e g. in maize, fowl, and mouse. Until recently only one linkage group, that in the sex chromosome, was demonstrable in man In 1951, however, linkage in a human autosomal chromosome was for the first time definitely demonstrated in the Copenhagen Institute for Human Genetics (*vide* p 51)

The theory of the linear arrangement of the genes in the chromosomes was finally proved in 1935 by a study of the so-called giant chromosomes occurring at the larval stage in the fruit fly and other fly species, particularly in the salivary gland cells In these big cells it can be seen how each chromosome presents a transverse striation, constant for the species concerned and brought about by the characteristic arrangement of the chromatin in the chromosome By crossing experiments, compared with cytologic investigations, it now became possible to show that the genes, in themselves ultravisible, are arranged in a certain manner in relation to the chromatin striation.

Recently an important new field of genetics, the *biochemical genetics*, began to develop The first biochemical genetic study was carried out by Garrod in his investigation on human alcaptonuria, published 1909 But more systematic biochemical genetic studies have only been carried through within the past ten years or so

The ascomycete *Neurospora crassa* has particularly often been used as an experimental object, but the genetics of yeast and bacteria have likewise been studied in connection with investigations of bacteriophages and viruses. It has been shown that the gene is the basis of synthetic chemical activities of the cell, and biochemistry will no doubt play an increasingly important rôle in genetics

Human beings are subject to the same fundamental laws of heredity as other living organisms This is the reason why the theories regarding human, including medical, genetics changed completely after the year 1900 In the wake

Holland, Correns in Germany, and Tschermak in Austria. Thus all at once they became universally known. Shortly after it was noticed that the distribution of the chromosomes during cell division gives a natural explanation to the Mendelian splitting, and that during sex-cell formation the chromosomes are distributed independently of each other in conformity with Mendel's laws These laws, which were discovered by statistical analysis of gross morphological characters, were now verified cytologically.

The rediscovery of Mendel's laws was soon followed by the discovery of two other facts, both of fundamental importance for the study of genetics: the non-inheritability of acquired properties and the existence of mutation.

In 1903 Wilhelm Johannsen published his investigations into the so-called "pure lines" in self-fertilizing plants. Acquired properties had previously been claimed to be inheritable (Lamarck's and Darwin's theory), but Johannsen disproved this theory He was the first to distinguish definitely between inherited and acquired traits The sum of all the inherited characters he called the *genotype* (from Greek *gennao* = breed) and its reaction with a given environment the *phenotype* (from Greek *phaino* = appear) For the hereditary unit he introduced the name of *gene*, for a sex-cell before the fertilisation that of *gamete* (from Greek *gamete* = conjugal partner), and for the fertilized egg-cell that of *zygote* (from Greek *zygoo* = connect, yoke) If 2 parallel genes are alike in an individual, this individual is called a *homozygote* (from Greek *homos* = equal, alike), if dissimilar, a *heterozygote* (from Greek *heteros* = different, strange) as regards this pair of genes

The demonstration of the non-inheritability of acquired properties contrasted with Darwin's theory of selection, which formed the basis of the doctrine of evolution. This remained unshaken, however, after the simultaneous discovery of mutation, *which might explain the hereditary variability conditioning* the theory of evolution

Hugo de Vries observed in 1903 that the genes change spontaneously *in plants He called these changes mutations But the importance of mutations* was not fully realized till 1927, when H J Muller showed that such can be produced experimentally Within recent years it has been found that mutation *is a frequent* cause of disease

During the first few decades of the present century Mendel's laws were further elaborated and added to, in the first instance by the American worker Thomas Hunt Morgan and his collaborators For their comprehensive crossing experiments, along with cytologic investigations, they used the fruit fly, *Drosophila melanogaster*, which is particularly fit for genetic studies They used an enormous number of flies within a relatively short term of years Each fly was closely examined, and these acute observers were able to detect

basis of Darwin's theories concerning the importance of natural selection for evolution, pictured to himself the fatal consequences for the human race when the effect of natural selection gradually is abolished by developments of civilisation. The infirm and inferior individuals will not be destroyed, and in many cases they show greater fertility than the strong and more valuable. With increasing wealth and improvement of medical science, hygiene, and public care a steadily decreasing number of the physically and mentally deficient will succumb, and such conditions of living are created for them that they are able to breed offspring, while at the same time the fittest reduce the number of their offspring. Something should, in Galton's opinion, be done to check this development He created the word eugenics (from Greek *eu* = good, well, and *gennao* = breed), by which he understood the study of the factors of a biological or social nature that may improve or impair the physical or mental qualities of future generations.

Galton was fully aware that the possibilities of practising eugenic theories were small, since little was known then of hereditary conditions in man. He therefore started comprehensive family studies and was the first to undertake systematic twin investigations As, however, the basal genetic laws were not yet known, he did not reach far by these studies, and eugenics consequently remained mainly speculative.

An interest in medical genetics did not develop till modern genetic studies had been started after the rediscovery of Mendel's laws. Eugenic measures could therefore not be properly used until the nineteentwenties

Eugenic principles soon reached to other countries from England, often undergoing certain changes on their way It is more than 50 years since the first sterilisation was performed on eugenic grounds in America, and shortly after sterilisation bills were enacted in some American States

Towards the end of the 19th century eugenic principles reached Germany, where the concept of racial hygiene was introduced This gradually underwent a very unfortunate development, a complete metamorphosis, culminating during the period of the Nazi regime

In the totalitarian state, where nationalism and chauvinism teemed, all consideration for the single individual was set aside for the benefit of state interests, and negative methods of racial hygiene were carried through unscrupulously and brutally At the same time obscure and fantastic theories developed of blood and race, of the supremacy of the Aryan race, of "Herrenvolk" etc Racial laws were introduced, which led to the most savage persecution of races Racial hygiene, as it was misused in Nazi Germany, fortunately disappeared with the collapse of "The Third Reich" in 1945

Eugenic statutory provisions had, however, been introduced in other

thrown into the background. It was misused by students of races, who were often led astray. Of late, however, anthropology has again obtained a footing within various fields. Anthropometric measurements are nowadays frequently used in medical science.

Many medical and social problems can be solved by the aid of *social anthropology. It can give information on the states of nutrition and health,* as well as on the entire physical development and growth of a whole population or of certain particular groups of it. It is therefore important for the State health service, the school medical service, etc. Sociology, including social psychology, and *cultural anthropology* have rendered valuable information of consequence to medical genetics.

In anthropological physiology the most amazing development has taken place within the domain of *blood groups* or blood types, starting from Landsteiner's discovery in 1901 of the ABO groups, and continuing with the MN groups, the A_1, A_2, A_3 subgroups, the P group, and many other groups, among which particularly the Rhesus groups with its numerous subgroups are noticeable Together with the taster-non-taster and the secretor-non-secretor allelomorphs, these monomeric, normal characters create new and surprising possibilities for genetic analysis, identification, and problems of parentage

The anthropometric methods have also become of importance within *constitutional pathology* and the study of the different types of constitution *and body. The study of constitutional pathology, defined rather vaguely, was* started by English clinicians at the turn of this century, and has since been taken up in all countries. Investigations of morbid types of constitution did not prove particularly fruitful, but have nevertheless contributed to an understanding of the pathogenetic importance of hereditary factors. Through Kretschmer's intuitive and artistic typology and characterology they helped to clarify the differences between the various normal bodily types. He demonstrated that various normal and pathological mental characters occur chiefly in individuals belonging to certain bodily types Sheldon dived further into the study of constitutional psychology and elaborated new methods for investigating the relations between somatotype on one hand and temperament and personality on the other.

Following on the study of constitutional pathology medical genetics gradually developed into a large and independent branch of medicine, being now one of the fundamental subjects of medical science

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of genetic prognosis have been calculated for a considerable number of diseases.

In biology and medicine, especially in genetics and demography, we have to make extensive use of statistics, as appears from the pioneer works of Mendel, Morgan, Johannsen, and numerous other writers. But we must bear in mind that in the natural sciences statistics, though a great aid, must always be of secondary importance. Primary observations and their exact description are all important. In medical genetics, for instance, we must primarily concentrate on diagnosing correctly and on collecting and selecting the material in the right way.

Comprehensive demographic investigations have been carried out in several countries and in various ways to ascertain the morbidity, especially the psychiatric morbidity of the average population. The morbid risks and gene frequencies of a great many hereditary diseases are well-known to-day.

Methods have been found for determining the mode of transmission of various diseases on the basis of the frequency figures in the different groups of relatives of *proponti* suffering from a certain disease. Statistical methods have also been used to investigate the evolution of dominance and recessivity and study the genetic structures of populations. Furthermore, statistical calculations have been carried out to ascertain whether linkage and crossing-over are demonstrable in humans, and to study the effect of intermarriage, isolation, assortative mating, differential fertility, and mutation in the population.

Twin investigations play *an essential* part in human genetics. The twin method has been extensively employed and has given valuable results; but it has certain limitations and so the results achieved must often be accepted with some reservation.

Nevertheless, by means of *twin investigations* very important information has been obtained concerning the influence of hereditary factors and the manifestation of the gene in a number of diseases and characters, e.g. mental deficiency, schizophrenia, manic-depressive psychosis, criminality, epilepsy, tuberculosis, diabetes, and congenital malformations.

The study of medical genetics is based to a large extent on *animal genetics*, e.g. in cancer research, in the question of heredity in malformations, endocrine disturbances, and other diseases, and in investigations into the mode of action and the mechanism of the pathogenetic genes during ontogenetic development. The study of human chromosomes and chromomeres in connection with medical genetics was yet only nascent.

The vast science of anthropology, which had reached a high standard of development during the latter half of the 19th century, was for some time

of the development of genetics as a whole, the past fifty years have seen an enormous progress in the study of heredity in human characters, abilities, defects, and diseases.

Within human medical genetics we meet, however, with numerous difficulties, which do not occur in experimental genetics, such as the small number of children in the human race, the long time of a generation, and the fact that crossing experiments are out of the question. Here we must rest content with the combinations of parents that occur spontaneously. Moreover, many diseases only manifest themselves at a certain age, the diagnosis may be difficult to make, and it is often impossible to verify in cases of deceased persons, unless an elaborate case record exists. Unknown illegitimacies and adoptions occur Furthermore we must bear in mind that humans to a great extent are able to control their environment

The study and analysis of hereditary characters in man require special techniques and methods, which have developed step by step during the past four decades.

In 1905 Farabee, by investigating some large families, proved that *brachydactyly* is inherited according to Mendel's laws as a monomeric dominant character Some years later Lundborg showed, in a very large family, that *myoclonus epilepsy* is a recessive character. Since then an increasing number of hereditary lesions have been studied on the basis of pedigrees and family histories Before the first world war Goddard investigated mental deficiency its causes and consequences, while Rüdin studied the inheritance of *schizophrenia*. At the same time it was discovered that the inheritance of normal characters in man likewise is governed by Mendel's laws This is shown particularly plainly in the study of hybrid races, developed by crossing of human races differing very distinctly from each other The first investigation of this kind was made by Eugen Fischer, who studied a group of half-breeds living in *Rehoboth*, a small town in South Africa, who were the result of the mating of Boers, chiefly of Northern race, with Hottentot women. In America Charles Davenport made similar observations in crosses of Whites and Negroes Various other hybrid races show the same conditions

If we collect a great number of pedigrees we may see that some characters and diseases are inherited by simple dominance, recessivity, sex-linkage, or conditioned dominance, while many others likewise obviously depend for their development on genetic factors, but present a more complicated inheritance.

Statistic-genealogical methods have therefore been elaborated and extensively used Such were first employed for the study of the inheritance of various mental diseases Using the *propositus* method the empirical figures

of genetic prognosis have been calculated for a considerable number of diseases.

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thrown into the background. It was misused by students of races, who were often led astray. Of late, however, anthropology has again obtained a footing within various fields. Anthropometric measurements are nowadays frequently used in medical science.

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Part I

THE BASIS OF HEREDITY

CHAPTER 2

GENES AND CHARACTERS

GENOTYPE AND PHENOTYPE The genes, which are transmitted through the gametes, are not recognizable as such. Living beings possess a number of properties which all depend partly on hereditary and partly on environmental factors It is the gene which is inherited, not the character.

The two essentially different factors characterizing man are heredity and environment The hereditary factors, except in case of mutation, are transmitted unchanged from generation to generation, uninfluenced by environment The properties characterizing individual humans depend more or less *on the environment* Each of these properties manifests itself as the result of the action of one or more genes under the existing external conditions. The sum of these is termed the *phenotype*, or the appearance of an individual. By the *genotype*, or genetic constitution, we understand the sum of all the genes found in a single individual The phenotype develops by the action of the environment on the genotype The genotype is not directly visible, being in fact an abstraction But we can nevertheless obtain a certain knowledge of it by analyzing offspring, ancestors, and other relatives; and in plants and animals also by crossing experiments.

A change of phenotype brought about by external conditions, and not inheritable, is called a *modification* There is great variation, resulting from modification in a population because of the very different environments of the individual A modification may *revert*, if it is not too firmly induced, but it may also become so fixed that it cannot be reversed. The result of this process is called a *persisting modification*. A child that has been underfed during childhood suffers lasting damage Many incurable [illegible] diseases and [illegible]

The c [illegible]

Greek idi [illegible] depending on environment, paratypic We distinguish between idiovariation and paravariation (= modification). Cor-

* hom [illegible]

European countries before they appeared in Germany, viz. in Switzerland and Denmark, and at a later period also in Norway, Sweden, Finland, Iceland, and Esthonia.

In these countries eugenic measures began their proper development on a purely medical basis, in connection with the progress being made within the fields of public care, and medical genetics, and in Denmark also by the establishing of a *Medico-Genetic Registry* (*vide* p. 311).

By eugenics or *Genetic Hygiene* we understand to-day the branch of medical science which aims at preventing the transmission of pathogenetic genes from one generation to the next, and thereby limits their spread in the population.

Eugenics belongs, in other words, to the purely medical subjects. Its sole task is that of preventing disease and the consequent suffering and calamity. It constitutes an essential part of preventive medicine. But there are still many countries in which eugenic measures are employed to a very limited extent only, or even not at all.

at 37°C no dye-stuff is produced. This change is exclusively phenotypic, for by further inoculation from the colourless culture dye-stuff is again produced at room temperature The so-called Russian rabbits are white except on the peripheral areas (tail, nose, ears, and paws), where the hairs are black, because the temperature here is slightly lower. If we shave part of the body and let the animal live at a low temperature, the new hairs growing will be black, and likewise the hairs on the peripheral areas will become considerably lighter, if the animal is kept at a relatively high temperature. The phenotype varies, in other words, with the environment. Similar observations may be made in man, whose development and course of life may be marked by his environment. On the other hand, hereditary factors may also be seen to exert their influence almost independently of environmental factors, as in the following instance

A woman, aged 24, was an illegitimate child Her father's family was unknown Her mother lived for many years as a prostitute. Her maternal grandmother was a habitual drunkard and a notorious whore She herself was in early infancy adopted by a childless, well-to-do master artisan and his level-headed wife, who gave her the best possible education during the childhood, and supported and guided her to the best of their ability during her youth At school she proved to be intelligent, but even by this time she displayed pronounced psychopathic traits, being very lazy, unreliable, capricious, and egocentric. At the age of 17 she left her good home to live as a prostitute She has since been a very active prostitute, who has had intercourse not only with numerous men, but also with many women, as she has a homosexual disposition as well The police have punished her in vain, 3 times with imprisonment and 12 times with fines, and her adoptive parents have by a more humane procedure, likewise unsuccessfully, tried to make her change her mode of life Examination of her mental state revealed her to be a pronounced psychopath with hyperthymic traits, and also to be hypersexual in addition to being a lesbian.

This is, however a selected instance Far more often the human phenotype has obviously developed by an intimate interaction of hereditary and environmental factors.

Take, for instance, the case where a father and his son, both buglers, were shown to be suffering from pulmonary emphysema This was not due exclusively to the environment, in this case the occupation, as not all b [illegible]

[illegible]

is [illegible] inheritance, which

per [illegible] nd "acquired" pro-

[illegible] always be an interaction of genotype and phenotype By these expressions we simply understand that one or the other of the two factors predominates Resemblance of parents and offspring, e g in behaviour, voice, manner, gait, writing, habits, dispositions, have been claimed to be false inheritance, due to conscious

respondingly a distinction has been made between nature and nurture as the antithesis between genotype and environment.

Clone, Pure Line, Population. Clones and pure lines afford the best possibilities of investigating the variation of the genotype in different environments.

A *clone* (from Greek *clon* = shoot or graft) comprises a group of organisms descended from a common ancestor by asexual reproduction If, for instance, we isolate a single bacterium and implant it in a culture medium the resulting growth of bacteria constitutes a clone. All variations within a clone must, apart from mutation, be due to modification and therefore be non-inheritable.

By *pure line* we understand the descendants obtained from self-fertilisation of a single homozygous parent (in modern usage also an inbred homogenic strain). In pure lines any variation is due to environmental factors By weighing beans belonging to the self-fertilizing species we find that the beans descended from one individual and having the same genes differ somewhat. Measured by their weights such beans are distributed approximately according to the normal distribution curve The majority are of middle size, but some are relatively big, *plus variants,* and some relatively small, *minus variants.* But in the next generation the average bean weights are the same irrespective of the weights of the mother beans, as long as these belong to the same pure line.

Pure lines do not occur, of course, among higher animals and humans Here the individuals that mate constitute a genetically heterogenous *population,* a mixture of different biotypes. Two completely alike individuals do not exist within a population The variation found is partly an *idiovariation* due to mutations or due to a *variation of combination,* owing to different combinations of the genes in the different individuals, and partly a *paravariation,* determined by different environments.

Human populations are always of a limited size. Their composition alters continually in an incalculable way by idio- and paravariation In a population, at least under present social conditions, unrestricted random mating (*panmixis*) does not occur.

Heredity and Environment. The interaction of hereditary and environmental factors is difficult, often quite impossible, to explain. They are complementary concepts. Instances may be mentioned, however, which throw a light on the significance of one or the other of these factors

Bacillus prodigiosus grows at room temperature in red colonies, whereas

tive descriptions, rather than about quantitative and qualitative characters The colour of the eyes has, for instance, been described as a qualitative character, whereas body height and body weight are more of a quantitative nature Mental properties, such as disposition, temperament, and intelligence, are mainly qualitative. The latter may, however, also be regarded as quantitative, when considering the possibilities of intelligence tests We may say that the qualitative differences are differences in kind and the quantitative differences in degree. But no sharp distinction can be made. Quantitative characters are generally more susceptible to environmental influence than qualitative.

Inheritable diseases are probably as a rule to be regarded as qualitative, especially if due to a single gene, but in some cases they are rather quantitative There is a gradual transition from illness to health, as known, for instance, from the different degrees of oligophrenia.

The *variability* of the various properties seen in living beings may be due to different causes

It may be a paravariability, due to *environmental* factors, which may produce different modifications.

Further, the variability, if qualitative, may be determined by different gene combinations owing to crossing of parents heterozygous for a greater or smaller number of gene pairs If more quantitative, the variability may, *indeed*, be caused by different gene combinations, but the genes concerned are then often homologous polymeric or multiple allelomorphic.

Finally, the variability may be due to mutation.

The study of the variability in man may be approached from different angles

We may describe the variability of the individual characters, study their incidence and dependence on age, sex, constitution, environment, etc., and furthermore, by twin investigations, determine the extent to which the variability depends on environmental factors *alone*. *Finally*, we may, through family investigations, study intrafamilial and interfamilial variability.

or unconscious imitation. Although there is some truth in it, there is no doubt that uniformity of the underlying genes produces a far more thorough similarity than can be obtained by imitation alone.

Some diseases, e.g. many physical deformities and mental defects, arise and develop practically uninfluenced by external conditions. These are the hereditary diseases in the more restricted sense. Other diseases, whose occurrence is also determined by hereditary factors, manifest themselves only under certain external conditions of life. Finally, some diseases, e.g. the traumatic ones, depend almost exclusively on the environment.

There is, in other words, no sharp line of distinction between inherited and acquired properties and diseases One and the same gene may present great variations of manifestation in different environments It is therefore difficult to distinguish between hereditary and non-hereditary diseases, and in numerous cases it is impossible to say whether the gene or the environment plays the greater part.

A somewhat fortuitous distinction has been made between *internal* and external conditions By *internal conditions* we understand the conditions within the organism which influence the possibilities of development of the individual gene, e.g the hormonal environment and the like In a certain race *of sheep the males always have horns whether the gene is present in the* heterozygous or the homozygous form, whereas the females have horns only if they are homozygous for the gene This is actually an instance of sex-influenced inheritance (*vide* p 92).

Among internal conditions we must also include the *genotypic milieu*. The individual gene is also influenced by the remaining genes present in the mosaic of genes, which differs for the different individuals Some genes can be active in one genotypic milieu, but not in another

The significance of external conditions can best be investigated by studying one-egg twins, as will be mentioned later The internal conditions, specially the genotypic background, are in the main alike in one-egg twins, and their significance cannot, therefore, be assessed by twin studies This can probably be done in other ways, e.g by examining the offspring of a great number of married couples where both partners of each couple have a certain recessive character in the homozygous form. If all the children possess this character, it must be relatively unaffected by the genotypic milieu

VARIABILITY It has been tried, though not always with success, to distinguish between qualitative and quantitative characters The terms qualitative and quantitative characterize our way of describing an entity rather than characterizing the entity itself We should speak about quantitative and qualita-

phase the nuclear membrane disappears and the viscosity of the cytoplasm surrounding the chromosomes increases Thereby the spindle is formed, which contains fibres parallel to the axis of the cell. Each chromosome often has a constricted area at which the so-called *centromere* or *kinetochore* is situated. By the end of the prophase each centromere divides into two and the chromosomes settle in the equatorial plane.

During *metaphase*, which is rather short, the chromosomes are plainly visible, and the two halves of each chromosome, called *chromatids* developed by longitudinal splitting of the chromosomes, are now separated from each other. During *anaphase* they wander towards the 2 poles of the cell, where 2 daughter nuclei, optically homogeneous, are reformed. The chromatids loosen their spirals, and the chromatin is distributed in the nucleus The chromosomes become less distinct, and a nuclear membrane forms round each group This is the beginning of *telophase*. The cytoplasm also divides, so now we have two new cells, each with the same number of chromosomes and the same hereditary elements as the mother cell

Meiosis. In all divisions, except the maturation divisions of the sex-cells, or meiosis, the chromosomes are arranged in pairs. The two partners of each pair are designated as homologous, and are of the *same size, shape*, and structure Originally one partner is derived from the father and the other from the mother of the individual concerned A human being thus contains in his cells two similar sets of 24 different chromosomes, one set derived from his mother, and the other from his father. At the maturation divisions, where the chromosome number is halved, the chromosomes are distributed in the manner that each gamete contains only *one partner from* each chromosome pair. During meiosis two divisions of the nucleus take place with only one division of the chromosomes

At the beginning of meiosis, the *leptotene* stage, the chromosomes are seen as non-split thin beaded threads *forming* strings of chromomeres. The homologous chromosomes come together in pairs side by side, chromomere by chromomere, a process known as *conjugation*, during the stage of pairing or the *zygotene* stage After pairing the chromosomes [illegible] [illegible] [illegible], where the [illegible] developed from a homologous chromosome pair, known as bivalents, are closely associated before they uncoil and fall apart in pairs, the two pairs being held together by exchange of partner among the threads. These exchanges are called chiasmata During the conjugation of chromosomes, the synapsis, the *crossing-over* takes place in such a manner that the chromatids

Chapter 3

HEREDITARY TRANSMISSION

1. *Mechanism*

Hereditary transmission from generation to generation occurs through the nuclei of the sex-cells (chromosomal inheritance) and, particularly as regards the ovum, also through the cytoplasm (cytoplasmic inheritance) The transmission of the genes through the nucleus is by far the best known and will therefore be described first.

A. *Chromosomal Inheritance*

The growth of an organism takes place both by the enlargement and the *multiplication of its constituent cells The multiplication depends on division* of the cells and the nuclei.

The division of the cell nucleus may be direct or indirect By direct *division, amitosis, nucleus and cytoplasm divide, without visible differentiation* of the nucleus into chromosomes By indirect division characteristic, morphologically observable processes occur in the nucleus, which fully explain the mechanism of inheritance

When the cell is at rest, i.e. undividing, the individual chromosomes are indistinguishable. The nucleus is enclosed in a membrane, within which we may sometimes see a network of linin or protein fibres, carrying chromatin granules In the nucleus one or two nucleoli or storage bodies are seen When the nucleus divides, the chromosomes become dense and stainable and are thus accessible to examination A number of chromosomes are found, which are characteristic of the species and in the main remain constant throughout all vegetative divisions. Only in the mature sex-cells are their number halved

The vegetative cell division is called mitosis (from Greek *mitos* = fibre), while the two last divisions before the formation of the mature sex-cells, the reductional division and the equational, are grouped under the name of meiosis (from Greek *meion* = smaller) Mitosis and meiosis differ in essential points and will therefore be described separately

Mitosis. At the resting stage of the cell, the interphase, the chromosomes are not visible, *but their individuality is preserved.*

At the beginning of ***prophase,*** the first stage of cell division, the chromosomes shorten and thicken by forming spirals Towards the end of the pro-

meiosis, where division occurs of the chromosomes' centromeres, which have hitherto remained undivided. Then follows the second metaphase and the second anaphase, during which the chromatids segregate as in an ordinary cell division.

Meiosis has thus produced four new daughter cells, each with a halved chromosome number In the male organism four equally large cells are pro-

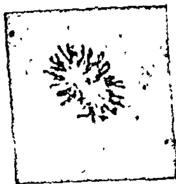




Fig 2—Mitosis in man. Metaphases 48 chromosomes.

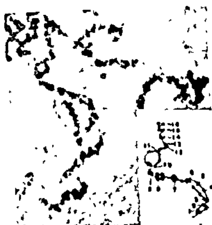


Fig 3—The Human Nuclear Chromosome from pachytene nucleus, Photomicrograph and diagram of the same chromosome 1-16 indicate chromomeres, perhaps also spiralization After Schultz and St Lawrence, Journ Hered, p 30, 1949

duced, while in the female only one fully developed egg cell is formed in addition to three polar bodies The polar bodies are much smaller than the egg cell, in mice, for instance, 30 to 40 times smaller. But we cannot exclude the possibility that a relatively well-developed polar body in rare cases may be fertilized

Fertilisation The sperm must penetrate the corona of cells surrounding the egg to be able to fertilize the egg. The head of the sperm carries an enzyme, hyaluronidase, which acts on the intercellular connective substance, hyaluronic acid, and enables the sperm to penetrate the surrounding cell layers of the egg quickly enough to win the race, i e to approach the egg before any

from the homologous chromosomes break at identical points, with exchange of chromatid segments containing a greater or smaller number of chromomeres. The breakage always occurs at a *point between the chromomeres, so that only* whole chromomeres (and whole genes, *vide* p. 28) are exchanged by crossing-over. The points of breakage are always found at a certain distance from each other. As a rule only two of the four chromatids cross over at each breakage



FIG 1.—Mitosis in body cells from human embryos To the left early prophase, to the right late prophase 48 chromosomes. Above photomicrograph, below diagram of the same cell division figure.

At the conclusion of the crossing-over the split chromosomes begin to move away from each other. The chiasmata are torn and the chromosomes shorten and place themselves just inside the nuclear membrane This is the stage of diakinesis, and here the chromosomes are fairly easy to count. Next the *nuclear membrane bursts, the nucleolus disappears, and the spindle is formed;* the first metaphase of meiosis occurs Now follows the first anaphase, where the homologous chromosomes, each consisting of two chromatids, segregate and move towards opposite poles. But owing to the crossing-over, the individual chromatids in some cases contain both paternal and maternal material The 2 nuclei formed during the anaphase enter into a short telophase, or pass directly into another division, with formation of the second prophase of

THE CHROMOSOME SET It has been mentioned that the number of chromosomes (from Greek *chromos* = colour and *soma* = body) is constant within a certain species. The number present in a mature sex-cell is called haploid (from Greek *haplos* = single). In the body cells the number is generally diploid, but occasionally there may occur more sets of chromosomes in a

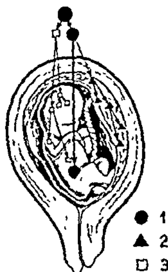


FIG 6—Diagram showing the continued transmission of the chromatin substance through succeeding generations. 1. The *germ track*, the lineage of cells in development of an organism, which are potent ancestors of germ cells, as opposed to somatic cells, leading from the gonads of parents to the gonads of their offspring through the generations 2 The trophoblast 3 The somatic cells 2 and 3 are formed anew for each individual, independent of the germ track

few or in all the cells of an organism; the chromosome combinations may be triploid, tetraploid, etc No definite system has been demonstrable for the numbers of chromosomes in different species. They vary considerably, as appears from the following table showing the diploid numbers in different animals and plants

Man (all races)	48	Rabbit	44
Monkey (Macacus)	48	Mouse	40
Hedge-hog	48	Fowl	66?
Horse	60	Fruit fly	8
Ox	60	Horse thread worm	2
Sheep	54	Potato	48
Dog	78	Wheat—Oats	42
Cat	38	Rye—Barley	14

Although there seems to be no definite system, we may in closely related plants find chromosome numbers that are multiples of certain cardinal numbers, e g. 7 or 9 This suggests a common origin of the related species The



Fig. 4.—Diagrammatic illustration of crossing-over during synapsis. The 4 chromatids are seen side by side. Different possibilities of crossing-over of the chromatids are indicated in the diagram (after Cleland and Brittingham)

other sperm When the first sperm has reached the egg no other sperm can enter. After the sperm has entered the egg, two nuclei, one from the sperm and the other from the egg, will for a short period, lie separate in the cytoplasm of the egg. These two nuclei will soon fuse, however, so that the fertilized egg, the zygote, has twice as many chromosomes as the gametes The chromosomes are again arranged in pairs with one partner of each pair derived from the fertilizing sperm and the other from the fertilized egg, which contain all the hereditary potentialities of the future child The hereditary influences of mother and father are approximately equal Through meiosis and fertilisation the chromosomes are, in other words, transmitted from generation to generation in the way that the individual partners, apart from crossing-over, are separated unblended from each other and then combined again freely at the sex-cell formation. In the individual sex-cell it is thus either the paternal or the maternal partner from each pair that takes part in the free combination In each chromosome pair one partner is always originally derived from the paternal and one from the maternal organism Thus, the transmission of the chromosomes corresponds exactly to that which Mendel suggested for the hereditary factors without having an exact knowledge of the mechanism of fertilisation

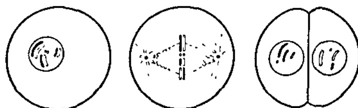


Fig 5—Meiosis, diagrammatically illustrated in individual with 4 chromosome pairs The chromosomes originating from the individual's father are black and those from the mother white. The diagram in the middle shows the chromosomes distributed in pairs in one of the 8 ways possible. The diagram to the right shows a similar distribution in the daughter cells

The discovery in 1935 of giant chromosomes in some big cells containing nuclei of an unusual size in the larval salivary glands of flies (*diptera*) and particularly of *Drosophila* facilitated the study of chromosome structure. These nuclei are in a kind of permanent prophase. They are called polytene



FIG 7.—The same segment of parallel chromosomes in giant cells of salivary gland from different flies of the same species × 2200 The same structure is seen in A and B, and in all individuals within the same species (after Metz)

nuclei, in which the protein production and gene reproduction go on at the same time These nuclei continue growing without ever dividing. Their chromosomes divide again and again inside the nuclei. They are represented by many linear, stretched, and paired threads They resemble cables consisting of parallel wires The chromomeres on the individual pairs of threads are situated opposite each other, therefore manifesting themselves as characteristic transverse lines across the chromosome, which resembles a banded ribbon.

The longest ones of the salivary gland chromosomes are about 0.5 mm long and 0.005 mm in diameter, i.e. almost 150 to 200 times as long as those in other cells The structure of these large chromosomes is now plainly visible under the microscope It is marked by a great number of transverse bands or

individual species may then present diploid, tetraploid, and hexaploid chromosome sets in relation to the cardinal number

No difference is demonstrable between the chromosome sets in the various human races. Accordingly they may all be crossed with each other. Occasionally the somatic cells present a chromosome number differing from the diploid. There are counts on record from various tissues which have lower or higher numbers than 48; but we must here bear in mind that it is difficult to count exactly the chromosome number in the body cells of higher animals. On the other hand, there is no reason to believe that the chromosome number should be absolutely constant within a species. It is the total number of genes or chromomeres, if you like, that matters, and not so much the number of chromosomes which are differentiated during cell division. In morbid tissue, e.g. neoplastic or inflammatory tissue, very considerable abnormalities in the cell divisions may occur, such as multipolar cells and chromosome numbers differing completely from the normal. We do not know whether human beings may exist with three or more chromosomes sets in all cells. However, among mammals, e g hog and rabbit, animals with three sets in all their cells have been bred experimentally.

The chromosomes change, as stated, in shape and size during mitosis, but they are generally described as they look at metaphase

The metaphase chromosomes may have many different shapes, ranging from ball shape by shorter or longer rods to thread shape The longish chromosomes may be bent in characteristic figures, e g V- or J-shaped At the monaster stage the big chromosomes often lie star-shaped in a ring, while the small ones lie within the ring (*vide* Fig 2) The chromosomes are to a certain extent identifiable by shape and size, as seen, for instance, in Fig 8.

The chromosomes also vary considerably in size, both from cell to cell and from one individual to the other The metaphase chromosomes in man and most animals are 1 to 5 μ, or 10 μ, at the most, long; and ½ to 1 μ in diameter It is therefore generally speaking impossible to study their finer structure even with the best microscopes using visible light rays In a number of cases it is, however, easy to see how the chromosomes are constructed of threads, which appear to be covered by a succession of fine beads, the chromomeres (Fig 3) The chromomeres occur in different sizes, arrangements, and numbers, which are constant for and characteristic of each chromosome of a species. The chromosomes never lose their identity in the nucleus They are indistinct thin relatively uncoiled threads during the period of non-division of the cell During the cell division they become greatly coiled and relatively thick At this stage highly stainable desoxyribose-nucleo-proteins are concentrated in considerable amounts on the chromosome thread, the chromonema

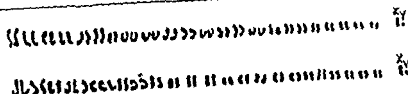


FIG 8—Human chromosomes arranged according to size, from male White (above) and male Negro 23 pairs of autosomes and XY-chromosomes.

(XY) If it is fertilized by a sperm cell containing an X-chromosome, the resulting individual will be female (XX).

GENES Each hereditary factor or gene constitutes to a certain extent a separate entity It determines a character in the adult organism. The genes act as units in the crossing-over, which occurs between them, but the crossing-over never takes place through a gene. At the formation of the gamete the two partners of a gene pair are separated unblended, after which the genes combine freely During mitosis each gene divides into two new genes of the same nature as the original one

The genes lie linearly arranged in the chromosomes, forming an array of interacting cellular constituents The genes carried in the same chromosome are linked The genes belong together in linkage groups, which are present in a number corresponding to that of chromosome pairs. The fruit fly has four linkage groups (*compare, however, p 49*) and maize ten. In many animals and plants a greater or smaller number of linkage groups are known During gamete formation the linked genes go together to the same gamete, unless crossing-over has taken place

The sites of the linked genes in the individual chromosomes can be determined to a certain extent, especially through crossing-over experiments, and the experimental results have later been confirmed morphologically

While previously the cell was regarded as the smallest biological unit, the genes are now the smallest units recognizable in the cell They are able to continue identical reproduction, as they multiply by simple division Their effect on the organism must be regarded as enzymatic in as much as they bring about comprehensive specific physiological processes But we cannot simply parallel the continued reproduction of the genes during cell division with the autocatalytic reproduction of the enzymes It seems more natural to compare the reproducibility of the genes with those of viruses or bacteriophages, i e they are able to multiply indefinitely in living tissue. This reproduction occurs, however, under a certain control, being dependent on the division of the cells Viruses may, like genes, undergo changes by mutation.

disks, constant in identical chromosomes in individuals belonging to the same species. Through crossing-over experiments, compared with morphological investigations, which show deletion, translocation, or inversion of chromosome segments, it has been found that the genes lie in the transverse bands found on the giant chromosomes The chromomeres corresponding to the transverse bands are present in a constant number along the chromosome threads. The genes, which are not visible, must be supposed to be located in the chromomeres, where they are surrounded by chromatin

Chromatin may be of different types. In some cells certain parts of the chromosomes remain stainable throughout the resting stage, being considered heterochromatinic, as opposed to the rest of the chromosomes, which are euchromatinic.

Some chromosomes contain chiefly heterochromatin, e g. the Y-chromosome in *Drosophila* and supernumerary chromosomes in many plants Heterochromatin is genetically inert, contains and produces a simple protein of a histone type, while euchromatin consists of and probably produces more complex proteins of globulin type.

Sex Chromosomes. It has been mentioned that the chromosomes are paired, and that the two partners are alike as regards shape and size, but naturally not always as regards hereditary contents, as two allelomorphs are not always identical However, one sex possesses a pair of chromosomes whose partners are *not* alike, as a rule either in shape or in size This is the sex chromosome pair, which thereby differs from all the other chromosome pairs, called the *autosomes*.

In one sex there are found two different sex chromosomes, named X and Y They constitute a pair and therefore become separated from each other by the reductional division, so that one half of the mature sex-cells contains an X-chromosome and the other half a Y-chromosome. The other sex has two X-chromosomes and can accordingly only produce gametes containing an X-chromosome At fertilisation equally often there are produced zygotes containing two X-chromosomes, and zygotes containing both an X- and a Y-chromosome The sex possessing two X-chromosomes is designated as homozygous, and that with one X-chromosome and one Y-chromosome as heterozygous.

In man and mammals, as well as in various lower animals, e g the fruit fly, the male sex is heterozygous, while in other animals, e g birds and butterflies it is the female sex that is heterozygous

If a human egg cell, which always contains an X-chromosome, is fertilized by a sperm cell containing a Y-chromosome a male individual is produced

Thus, the nucleus may be regarded as a differentiated stable and balanced system of protein-producing units, in contrast to the less organized and more unstable cytoplasm This explains why the control of inheritance and development is attached mainly to the cell nucleus The gene is the basis of the synthetic chemical processes in the cells, and thus in the whole organism, e g. of the syntheses of various important organic substances, such as amino acids, nucleoproteins, and vitamins. The cytoplasm feeds the nucleus with the materials from which it builds up its specialized structures, and, on the other hand, the chromomeres produce the substances regulating the growth and development of the organism

Gene Action. The genes control the processes of cellular metabolism and the synthesis of protein and other organic chemical compounds.

The substances produced by the genes are conveyed from the nuclear system to the cytoplasm, where they interact with the products of other genes and with cytoplasmic material. Here begins the interplay of gene action and environment which later continues beyond the individual cell and determines the differentiation of organs and tissues and the whole development of the individual.

The nuclear system depends for its propagation on the desoxyribose nucleic acid and on the protein fibres of its chromosomes for its permanent existence. The linearly arranged genes in the chromosomes are of several kinds, lying between two extremes: the small determinants are represented by heterochromatin and the large determinants with the more complex products, are represented by euchromatin Between these two extremes we find intermediate and transitional forms

The properties are thus a result of a complex interaction of genetic and environmental factors

Biochemical genetics has, however, shown that the actions of some of the genes are rather simple Recessive alcaptonuria in man is due to an inability to destroy homogentisic acid by oxidation Numerous other metabolic diseases in man depend, as will be described later, on the failure to produce a single enzyme, causing a characteristic disturbance of the metabolic processes The Dalmatian dog has a single recessive gene which prevents an enzyme oxydizing uric acid to allantoin, thereby causing increased excretion of uric acid in the urine

In a number of lower organisms, such as the fungus *Neurospora crassa*, single-gene recessive mutants can be produced which are unable to synthesize certain substances, e g amino acids, vitamins, pyrimidine bases, etc

Within recent years a distinction has been attempted between three different gene types major genes, polygenes, and supergenes

They contain nucleoproteins, which is also a characteristic constituent of chromosomes. Somé virus species are nucleoproteins, which can be prepared as crystalline proteins with a molecular weight of up to a few millions.

THE CHEMICAL STRUCTURE OF CHROMOSOMES AND GENES. An attempt has been made to understand the chemical structure of the genes. The cell nucleus consists chiefly of nucleoproteins

Nucleoprotein is a protein combined with nucleic acid. Nucleic acid is a product of the polymerisation of nucleotides The nucleotides consist of a purine or pyrimidine base, ribose, or desoxyribose carbohydrate, and phosphoric acid Thus nucleic acid may be either ribose nucleic acid or desoxyribose nucleic acid The complex protein desoxyribose nucleic acid is only found either attached to the chromosomes of every animal and plant, or, in lower organisms, such as bacteria and viruses, distributed in the cytoplasm, probably representing a nuclear element genetically analogous to the chromosome. This primitive chromatinic element divides at the moment of cell division.

It can be shown by ultraviolet spectroscopy that during cell division nearly all the nucleic acid is attached to the chromosomes The metaphase chromosomes contain protein, being attacked by proteolytic enzymes. Some of the proteins are formed from fibrous elements consisting of chains of polypeptide links in linear arrangement This chain may be single or multiple and highly folded, in the resting nucleus. In other types of proteins, the globular proteins, the molecules seem more spherical

The repeat distance in the stretched polypeptide chain is about 0 33 mμ (= 3 3 Angstrom units), or almost the same as the distance between neighbouring nucleic acid residues, i e the repeat units of which protein crystals are built

The size of the gene has been calculated to be between 10 to 100 mμ in diameter; the estimated maximum dimensions are 10 × 20 × 20 mμ. The lowest crossing-over percentage seen in *Drosophila* is 0 2 centimorgan (*vide* p 49), which corresponds to an about 10 to 20 mμ space for each gene. The genes are, in other words, presumably of the size of medium-sized protein molecules, and considerably smaller than many viruses and bacteriophages

The gene is perhaps a compound of a number of identical subunits The sensitive volume for gene mutations has been estimated at 1 mμ in diameter Thus the gene is possibly not the smallest biological unit

The chromomeres are supposed to represent or to include the genes, and they produce complex proteins. The small heterochromatin units produce fairly simple proteins together with ribose nucleic acid, while the larger more closely paired euchromatin chromomeres produce rather complex and specific globulins together with desoxyribose nucleic acid.

different external conditions one and the same gene may produce different characters (heterophény) On the other hand, one gene may influence the development of several different characters, a phenomenon designated as pleiotropy (polypheny). However, strictly speaking each gene has a pleiotropic action in that it theoretically has an influence on all characters, though on most of them only to a very small extent. It is the total genotype, the mosaic of genes, if you like, whose genes, by reacting on each other in a given environment, produce the phenotype, the sum of all the characters of the individual.

Whether a gene manifests itself, and to which extent, depends on various conditions.

First it depends on the properties of the gene itself, which may be strong and stable or weak and unstable Secondly other defined genes influence the intensity of manifestation of the gene concerned. Such genes, termed inhibitors or modifying genes, probably often belong to the polygenic systems Thirdly the effect of the gene depends on the environment and the genotypic milieu.

The variability of the gene effects may manifest itself in the penetrance, expressivity, and specificity of the gene

By the *penetrance*, rate of frequency or manifestation rate, of the gene we understand the proportion of possessors that are distinguishable from the unmutated normals The penetrance is often expressed in per cent, and may vary from 100 per cent to a very low figure.

The *expressivity* means the quantitative differences seen in the development of the character produced by the gene. The manifestation of the gene varies in degree Some human genes are very variable in their expressivity, e g many malformations as well as osteogenesis imperfecta (fragilitas ossium) (*vide* p 209) The variability may be inter- or intrafamilial.

Specificity is the name for the variation in the actual qualitative nature of the gene effects, giving a variation not in the amount of the final effect, but in its kind The specificity is strong, when there is a close relationship between a certain gene and a certain character

If a dominant gene has a manifestation rate under 100 per cent, it is said to present uncertain, varying, failing, or irregular dominance. There are found many hereditary diseases due to an irregularly dominant gene They may very well skip one or more generations, thus presenting a mode of transmission reminiscent of recessivity, though, of course, with a different distribution in the groups of relatives of the propositi. The manifestation rate can be determined by twin investigations. Recessive genes may likewise show failing manifestation, even when present in the homozygous form.

The *major genes* are genes whose differences or mutations are great enough to be identified by their individual effects. They correspond to genes or hereditary factors in the classical sense, and are present in the euchromatin, in the chromomeres, which contain large determinants with complex products. These genes determine in the main the development of the normal genotype. They are said to form the backbone of the organism.

Mutation of the major genes occurs by change of a single locus, a point mutation, which ordinarily is absolute in a qualitative sense. Most of the major gene mutations are harmful, giving rise to the typical hereditary diseases and abnormalities

The *polygenes* are genes whose differences or mutations are too slight to be identified by their individual effects. They are included in polygenic systems of genes having effects similar and supplementary to one another (comp polymeric genes p. 53). They are small determinants with simple products, small proteins and ribose nucleic acid They occur chiefly in heterochromatin, but may also be present in euchromatin. Polygenes may cause continuous variations, and they often determine the development of predispositions to diseases, as for instance tuberculosis

Supergenes are groups of genes transmitted as single units and situated along a segment of chromosome The 3 closely linked Rhesus loci and the M, N, S, and s blood group genes have been mentioned as instances of supergenic systems. Supergenic action is often due to chromosome re-arrangements and abnormalities. In animal experiments anencephaly and spina bifida may sometimes be due to chromosome re-arrangements Malformation syndromes may be ascribed to supergenes A single major gene may, however, by pleiotropic action cause a similar variety of effects

The total number of gene pairs or of gene loci in man is unknown Probably it is *relatively* small It has been estimated at between 10,000 and 80,000 genes Recently the 48 human chromosomes were calculated to contain 44,000 pairs of genes, but the exact figure cannot, of course, be given

THE VARIABILITY OF GENE EFFECTS Genes may to a certain extent be regarded as independent units, although varying in dependence on the rest of the genotype and the environment The allelomorphs co-operate in a special way; and the genes carried in the same chromosome are connected both morphologically and functionally. But all the remaining genes likewise interact, in as far as each gene displays its action dependent on the genotypic milieu of the entire organism and acts as a unit in the mosaic of genes

Each gene is mainly concerned with one character only. However, under

PLASMAGENES AND VIRUS. By hybridisation of inbred strains of mice with high and low mammary tumour incidence the predisposition to breast cancer has been proved in these mouse strains to be inherited exclusively through the mother. It has been suggested that this is due to cytoplasmic inheritance. However, further investigations have shown that transmission of the tendency to cancer takes place neither by plasmagenes in the cytoplasm nor through the placenta, but through the milk of the mother or the foster mother. It has been shown that the milk from mothers of high-tumour strains contains a factor, called the milk agent, which acts on the young in such a way that a large *proportion* develop breast cancer later in life. This milk agent is supposed to have the character of an (autochthonous ?) virus, and so must be placed on the borderline between hereditary and infectious agents.

There is found a great variety of species or strains of virus The virus particles, which are ultravisible and ultrafiltrable, differ in shape, from spherical to rod- or thread-shaped The sizes of the spherical virus particles range from 150-175mμ in diameter, e g the vaccinia virus, to 20-30 mμ or even smaller Bacteriophages, the virus of bacteria, may be 10 mμ or less The larger viruses are complex in chemical structure, containing desoxyribose acid, fat, carbohydrate, and other compounds. The *simpler* viruses contain protein with ribose nucleic acid attached.

The virus develops in the cells, just like nuclear genes or plasma-genes, which together form the genotype Virus may, however, be isolated from cells and tissue, and precipitated as crystals The virus particles are often infectious and not necessarily, like the genes, compatible with the organism of which they form a part

The study of the genetics of cancer elucidates the relation between viruses and genes Much evidence has been obtained through transplantation experiments

In mammals tumours can only be transplanted by whole cells The transplanted cells are genetically changed and have specific properties of producing tumours from certain tissues and of a certain histological structure. The spreading through the body occurs by a constant lineage of cells dependent on the genetic structure of the transplanted cells and the genetic composition of the host Tumours induced by carcinogens or arising spontaneously are probably spread in the same way

In fowl various spontaneous tumours, e g Rous' sarcoma, can be transmitted by injection of a filtrable *virus* The particles of this type are not infectious and can only be transmitted artificially.

As for the above-mentioned breast cancer of the mouse, it is conditioned by the combined action of genetic factors and the milk agent, dependent on the hormonal activity and the race or strain of the mouse Gene differences control the susceptibility of the mammary tissue cells.

B. *Cytoplasmic Inheritance*

PLASMON AND GENOME. As appears from what has already been stated, we possess a rather detailed knowledge of the inheritance taking place through the genes in the chromosomes, to which the majority of the hereditary characters are most likely attached. But a certain hereditary transmission also occurs through the cytoplasm, as observed particularly in plants.

We distinguish between plasmon and genome, denoting the hereditary agents transmitting characters through cytoplasm and nucleus respectively. In determining phenotypic characters the plasmon depends on the presence of certain genes. On the other hand, some genes are plasmon sensitive The same genes act differently in different plasmons Some experiments indicate differences in mutation rate in different plasmons, a circumstance to be considered in the study of evolution.

Hereditary transmission through the cytoplasm may take place partly through it as a whole and partly through formed elements present in it.

The cytoplasm of the cell contains plastids and chondriosomes, formed elements which divide with a certain regularity simultaneously with the cell nucleus. The plastids are self-propagating bodies associated with pigment production (chlorophyll, carotin). They occur only in plant cytoplasm They *may grow, divide, and be independent carriers of hereditary characters.* Presumably they may also mutate. They are most often transmitted by the egg, but may also be transmitted by pollen, even if this has only a very narrow border of cytoplasm. By plastid inheritance a segregation may occur in the offspring, but not in Mendelian numerical proportions To the plastids are attached bodies, plastogenes, which are proteins with nucleic acid of the ribose form attached. They probably include proteins important in development and differentiation.

Chondriosomes are found in both plants and animals We do not know whether they may carry hereditary characters, but this cannot be excluded. They propagate by division They may, perhaps, also be formed directly from the cytoplasm The plastids possibly develop from them

Plasmagenes are gene-like particles in the cell, but outside the nucleus, transmitted by the egg, or more rarely by the sperm The cytoplasm as a whole may also possess a hereditary character. A general quality of the cytoplasm may be transmitted purely maternally. As, however, the cytoplasm is evenly distributed over the daughter cells, no splitting can take place.

We know no unquestionable instances of cytoplasmic inheritance in man or higher animals But an attempt has been made to explain certain cases of maternal inheritance on the assumption that this exists.

CHAPTER 4

HEREDITARY TRANSMISSION

2. *The Laws*

The genotypic variation in a sibship is due to different combinations of the parents' genes in the offspring. It was Mendel who discovered the laws applying to the segregation of properties in the offspring of two parents. In his crossing experiments with the garden pea he studied the inheritance of a few characters so simple that each is due to a single gene only. He therefore actually investigated the transmission of the individual genes by crossing varieties or races within a certain species, e g tall garden pea with short. It was simple single factor inheritance.

By studying the assortement of types in the filial generations he observed that the individual characters, or genes, are inherited as mutually independent units which [illegible]

[illegible] from its mother. The two genes of a gene pair, occurring alternatively in the gametes, are also designated as allelomorphic (from Greek *allelon* = mutual and *morphe* = figure, shape) or allelic. The two allelomorphs of a gene pair are often symbolized by letters, e g. AA, Aa, or aa. If the two genes of the pair are alike, it is called homozygous (AA or aa), if different heterozygous (Aa)

If one gene, A, in a heterozygous pair, Aa, dominates completely over the other, so that AA and Aa are alike, the gene A is termed dominant and the gene a recessive. By crossing a purple garden pea variety with a white the flowers of the hybrid will, in case of full dominance, have the same colour as the purple parent But if A does not dominate completely over a, the hybrid will have pink flowers, and it is then called *intermediate* with regard to the character concerned If Aa comes close to AA, it is, however, more correct to speak of *prevalence*. Finally, two allelic heterozygous genes may each produce its own character and are said to have a *combined* or additive effect, as for instance the blood group genes A and B or M and N in the types AB and MN

MENDEL'S LAWS Mendel's laws may be summarized as follows·

1) When the germ cell is formed 2 allelomorphs are always separated unblended, but are combined freely with the other genes, except in case of linkage

Development of cancer is determined by the interaction of genetic and environmental factors.

We know many coxgenous tumour-exciting factors, such as irritation of the cells or tissues by trauma, chemical, thermal, or ray influence, parasites, bacteria, and viruses. These factors will probably in some cases cause somatic nuclear mutation But in all cases changes occur at the same time in the self-propagating proteins in the cytoplasm, which perhaps could be designated as mutation of the plasmagenes

PERSISTING MODIFICATIONS AND AFTER-EFFECT. *In some organisms, e g., Drosophila,* changes can be produced which are inherited in the female line for some generations and then are gradually lost They are probably caused by persisting, but not unalterable, changes in the cytoplasm. The mutant plasmagene does not possess the hereditary staying power of a mutated nuclear gene Such changes have been called persisting modifications or dauer-modifications (comp. p. 17).

Cytoplasmic inheritance must not be confused with the so-called after-effect or *paraphoria* In cases where the whole soma is under radical influence of some kind, the sex-cells may also be affected This may mark the first and possibly also the following generations as an "after-effect". There is no doubt that conditions severely affecting the whole organism, e g intoxications, may act on the foetus during pregnancy. Whether they may also, like proper "germ poisons", influence the germ cells in the non-pregnant organism is difficult to say for certain, but most likely they do. This would be a pseudo-Lamarckian effect. The theory has been advanced that iodine deficiency, for instance, may have a deleterious effect if present through several generations In a family which has moved to a district with endemic cretinism, endemic goitre will prevail in the first generation, but in the following generations we find an increasing frequency of deafmutism and fully developed cretinic degeneration

Summarizing we may say that cytoplasmic inheritance also undoubtedly occurs in man, but that we do not know the significance of this phenomenon.

By crossing 2 pea plants with yellow, smooth peas, which are both heterozygous for these 2 characters, yellow pea colour dominating over green and smooth peas over wrinkled, we get the following numerical distribution of peas in the offspring: 9 yellow smooth, 3 green smooth, 3 yellow wrinkled, and 1 green wrinkled.

Similarly 3 gene pairs will in the 2nd filial generation give 64 ($= 2^6$) gamete combinations, 4 gene pairs 256 ($= 2^8$) . . ., n gene pairs 2^{2n}. As a general rule n gene pairs give as follows in the 2nd filial generation:

2^n gamete types.
2^{2n} gamete combinations
3^n genotypes
2^n phenotypes, if one gene in each pair is completely dominant.
3^n phenotypes, if no gene presents full dominance.

3 gene pairs will in the 2nd filial generation, with full dominance of A, B, and C, give 64 gamete combinations distributed in the following phenotypes: 27 ABC, 9 ABc, 9 AbC, 9 aBC, 3 Abc, 3 abC, 3 aBc and 1 abc.

4 gene pairs will in the 2nd filial generation, with full dominance of A, B, C and D, give 256 gamete combinations distributed in the following phenotypes

81 ABCD	9 ABcd	3 Abcd
27 ABCd	9 AbcD	3 aBcd
27 ABcD	9 AbCd	3 abCd
27 AbCD	9 aBCd	3 abcD
27 aBCD	9 aBcD	1 abcd
	9 abCD	

Similar calculations can be made with a larger number of gene pairs.

The inheritance of dominant and recessive diseases can be directly inferred from the above laws

DOMINANCE. Any disease due to a dominant gene manifests itself in an individual even if the gene is inherited from one parent only As most inheritable diseases are comparatively rare, the genes for such are not particularly widespread in the population Anybody who suffers from a dominant disease will therefore as a rule have received the gene for it from one parent only Hence he transmits the gene to no more than half of his offspring. A dominant disease never skips a generation; it must manifest itself in each of them, and in on an average 50 per cent of the offspring, when one parent has the disease

Mating of two parent organisms, both homozygous for a certain character, but mutually different, will result in offspring which all present this character: the crossing of

AA ~ aa

forms the gametes A and a, which can only be combined into

Aa, Aa, Aa, Aa, . . . ,

i e. individuals that are all phenotypically and genotypically alike.

By crossing, for instance, a pea plant with yellow peas (AA) with one having green peas (aa) we get a hybrid (Aa) which has yellow peas like one parent, because the gene for yellow peas dominates completely over that for green peas. The result is the same whether A comes from the father or the mother.

2) In the next generation, the second filial generation, a segregation takes place into different types, the hybrid being able to form two gametes, A and a *The segregation occurs as indicated in the following table*.

The crossing of Aa ~ Aa gives equally often the 4 gamete combinations.

AA, Aa, aA, aa, i e

2 different phenotypes: 3A and 1a, if A dominates completely over a, and

3 different phenotypes. *1AA, 2Aa, and 1aa, if A does not dominate completely over a,* and

3 different genotypes · 1AA, 2Aa, and 1aa

Crossing of a yellow-pea plant with a green-pea plant gives yellow and green offspring in the proportion of 3 to 1

3) If two individuals heterozygous for two or more gene pairs are crossed, the partners of each pair are separated unblended, but one gene of each pair is combined freely with the genes from the other pairs The double heterozygote AaBb can produce the gametes AB, aB, Ab, ab Crossing of

AaBb ~ AaBb

therefore gives 16 (2^4) gamete combinations, all in equal proportions.

In case of full dominance of A and B we get

genotypes	phenotypes
1 AABB, 4 AaBb 2 AaBB, 2 AABb	9 AB
1 AAbb, 2 Aabb	3 Ab
1 aaBB, 2 aaBb	3 aB
1 ab	1 ab

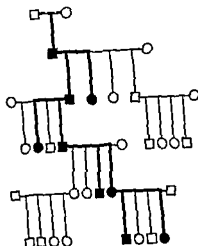


Fig 9—Dominant inheritance. Remark no skipping Half of the offspring are affected where one parent has the disease. The notches in the uppermost horizontal line indicate that the dominant disease has arisen by mutation

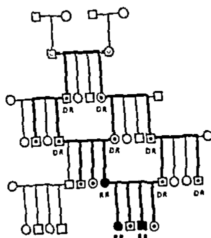


Fig 10—Recessive inheritance.
○ ⊡ carrier of the gene (DR)
● ■ affected (RR)
The notches in the uppermost horizontal line indicate that the recessive disease has arisen by mutation.

2) If one parent has the disease and the other is a carrier, 50 per cent of the offspring get affected, and 50 per cent become unaffected carriers:

$$Ss \sim ss = Ss + ss$$

3) If one parent has the disease, while the other is normal, all the children become carriers

$$SS \sim ss = Ss$$

4) If both parents are carriers (e g if one of the father's and one of the mother's parents has had the disease, or if the parents themselves have previously got a child with the disease) there is 25 per cent chance that the next child will be affected and 50 per cent chance that it will become a carrier

$$Ss \sim Ss = SS + 2\,Ss + ss$$

5) If one of the father's and one of the mother's parents are certain carriers (as may possibly appear from the data of his or her ancestors or descendants) there is 6 25 per cent (1/16) chance that the child will get

In the case of a *dominant* disease the morbid risks[1] for the offspring are as follows:

1) If one parent has the disease in the heterozygous form, there is 50 per cent chance that the child will get it, as appears from the formula

$$Ss \sim ss = Ss + ss,$$

where S is the dominant gene for the disease and s the normal allelomorph

2) If the father or/and the mother has inherited the gene for the disease from both parents (is a homozygote) there is 100 per cent chance that the child will get it:

$$SS \sim ss = Ss \text{ or } SS \sim Ss = SS + Ss \text{ or } SS \sim SS = SS$$

3) If both parents have the disease, there is either 75 per cent or 100 per cent chance that the child will get it:

$$Ss \sim Ss = SS + 2\,Ss + ss \text{ or } SS \sim Ss = 2\,SS + 2\,Ss \text{ or } SS \sim SS = SS$$

4) If none of the parents has the disease the child will not get it, even *if it occurs in other relatives.*

RECESSIVITY. The diseases due to recessive genes manifest themselves only if the gene concerned is received from both parents, not if received from one parent alone. Hence recessive genes may be transmitted through several generations without being discovered If 2 unaffected carriers (conductors) marry, on an average 25 per cent of the offspring get the disease, while 50 per cent become carriers, and the remaining 25 per cent neither get the disease nor become able to transmit it to their offspring The recessive diseases are therefore found to be widely scattered in families, often skipping generations, and manifesting themselves particularly in families where intermarriage has occurred.

In the case of a *recessive* disease the morbid risks for the offspring are as follows:

1) If both parents have the disease, there is 100 per cent chance that the child will get it, as appears from the formula

$$ss \sim ss = ss,$$

where s is the recessive gene for the disease, while S is the normal allelomorph.

[1] All the figures indicating risks in the following are, of course, average values presupposing full manifestation of the genes concerned

the abnormal recessive gene. In females, on the other hand, these characters manifest themselves only when the gene is found in both X-chromosomes. They are generally inherited through unaffected females to affected males, and are far more frequent among males than among females The father's X-chromosome is transmitted exclusively to his daughters and his Y-chromosome to his sons, whereas the mother's X-chromosomes are equally distributed between sons and daughters.

In the case of a sex-linked (X-linked) recessive disease the morbid risks are as follows:

1) If both parents have the disease there is 100 per cent chance that the child will get it, as appears from the formula

$$X_S X_S \sim X_S Y = X_S X_S + X_S Y,$$

where X_S is a X-chromosome containing the recessive pathogenetic gene.

2) If the mother has the disease and the father is normal, all sons become affected, and all daughters unaffected carriers:

$$X_S X_S \sim XY = X_S X + X_S Y$$

3) If the mother is an unaffected carrier and the father affected, 50 per cent of the sons will be affected, while 50 per cent of the daughters will be affected and 50 per cent carriers:

$$X_S X \sim X_S Y = X_S X_S + X_S X + X_S Y + XY$$

4) If the mother is an unaffected carrier and the father normal, 50 per cent of the sons will get the disease, and 50 per cent of the daughters become carriers

$$X_S X \sim XY = X_S X + XX + X_S Y + XY$$

5) If the mother is normal and the father affected, all the sons will be normal and all the daughters carriers:

$$XX \sim X_S Y = X_S X + XY.$$

The disease is as a rule transmitted from generation to generation through an affected male's unaffected sisters, of whom 50 per cent are carriers, or through an affected male's unaffected daughters, who are all carriers, to their sons Exceptions to this latter rule have been claimed in the past, but are now considered injustifiable

Dominant X-linked characters occur, of course, most frequently in the homozygous sex

We know various instances of X-linked inheritance in man, e.g colour-

the disease and 37.5 per cent (6/16) chance that the child will be a carrier. If the grandparents have the formula

Ss ~ SS

50 per cent of the parents will have the formula Ss and 50 per cent SS.

Parent combinations	Offspring
Ss ~ Ss	1 SS + 2 Ss + 1 ss
Ss ~ SS	2 SS + 2 Ss
SS ~ Ss	2 SS + 2 Ss
SS ~ SS	4 SS
	9 SS + 6 Ss + 1 ss

The percentage figures stated in item 5) apply only if the gene has not been introduced into the family through more ancestors than those mentioned. This state of affairs is likely to be present in cases of rare diseases, but where relatively frequent recessive diseases are concerned the proportion of carriers in the population is high (*vide* p 122). This fact must be taken into consideration in the calculation of the morbid risk in cases where the exact data of one parent only are available, showing, for instance, that he or she is a carrier or is affected with the disease. In the case of intermarriage this must always be taken into account when calculating the morbid risk of recessive diseases

Sex-Linked Inheritance The genes carried in the sex chromosomes are designated as sex-linked and inherited according to special rules. The genes in the Y-chromosome produce the Y-linked characters, present only in the heterozygous sex (the male in humans). We have many instances of Y-linked inheritance in plants and animals It is often called one-sided masculine inheritance if the male sex, and one-sided female inheritance if the female sex is heterozygous If a male has an Y-linked character, the gene for this will be inherited by all his sons, grandsons, etc

Y-borne genes behave as if dominant, but it is not justifiable to call them dominant, as they do not constitute partners in pairs of heterozygous allelomorphs Such single-allelic genes have been termed hemizygous. Y-linked inheritance has not been demonstrated with certainty in man But some diseases (ichthyosis, hypertrichosis of the ears, webbed toes) appear in a few families to show one-sided masculine inheritance

X-linked recessive characters manifest themselves in the heterozygous sex as dominant characters, appearing even if the gene is present singly, as there is only 1 X-chromosome, and thus no normal allelomorph to suppress

Cytological investigations on animals, e g. *Drosophila* and rat, have shown that the X- and Y-chromosomes pair during meiosis, but only in a limited region of each There exist homologous paired segments of the X-and Y-chromosomes, and non-pairing, non-homologous regions called the differential segments The theory has been advanced that the sex-chromosomes in man should behave in a similar way. Incomplete sex-linkage should thus also be possible in humans, because genes which might show crossing-over should occur in the homologous paired segments of the X- and Y-chromosomes Dominant sex-linked retinitis pigmentosa, recessive sex-linked xeroderma pigmentosum, total colour-blindness, epidermolysis bullosa, and a few other rare diseases may be mentioned as instances of such incomplete sex-linked characters This theory cannot yet be regarded as proved, however.

The X-borne genes constitute the first linkage group known in man. The results of investigations into families in which both colour-blindness and haemophilia are present give evidences that crossing-over between the differential segments of the two X-chromosomes may occur in females.

Chapter 5

LINKAGE AND CROSSING-OVER

As stated previously, the genes carried in the same chromosome are said to be linked A number of linkage groups has been found to correspond to the number of chromosome pairs in the species concerned, in the heterozygous sex; and in addition extra linkage groups corresponding to the X- and possibly the Y-chromosome

At the gamete formation linked genes go together to the same gamete. Thus, they do not, like other genes, segregate and combine freely in the offspring Certain gamete classes, which would occur in case of free combination, are not produced, while others become more frequent The linkage may be complete or absolute. The linked genes then always go together at the gamete formation It may also be incomplete or partial, i e the linked genes do not always go together Certain gamete classes become more frequent and others rarer than would have been the case if independent segregation had taken place

Partial linkage is due to crossing-over (German· *Faktorenaustausch*). During meiosis, at the pachytene stage (*vide* p 23) chromosome segments

blindness for red and green, which is due to a recessive gene. The abnormality is inherited in the manner characteristic of sex-linked characters, being therefore far more frequent among males (5 to 8 per cent) than among females (0.25 to 0.5 per cent).

If q is the frequency in the general population of X-chromosomes carrying the gene for colour-blindness and $p = 1-q$ that of normal X-chromosome, then a man will have the probability q for being colour-blind. The frequency of homozygous females having the gene for colour-blindness in both X-chromosomes and therefore being colour-blind will be q^2. If the incidence of colour-blind males in a population is, for instance, 5 per cent, the frequency of colour-blind females will be 0.25 per cent; and if 7 per cent of all males are colour-blind, there should be about 0.5 per cent colour-blind females. The ratio of affected males to affected females is nearly, but not exactly $q:q^2$, because not all kinds of colour-blindness are of the same type (*vide* p. 228).

Haemophilia is likewise X-linked and due to a recessive gene. This disease does not, however, manifest itself in homozygous females, presumably because the female zygotes having the gene in the homozygous form are not capable of development.

The dominance of the normal allelomorph corresponding to an X-borne recessive gene is not always complete. The same applies to many dominant autosomal genes. The recessive gene is often demonstrable in a moderate form in a number of the heterozygous individuals. Females who carry the gene for colour-blindness in one X-chromosome as a rule have normal colour vision, but some of them present poor colour aptitude; their colour perception is not the same as in normals. Similarly female carriers of haemophilia often present prolonged coagulation time, and in some cases even an increased tendency to haemorrhage.

We also know a sex-linked form of hereditary diabetes insipidus. In these families the female carriers are in the main symptom-free; but some of them present deficient power of concentration of water, and if they get pregnant they may often, during the latter half of their pregnancies, have symptoms of diabetes insipidus, which disappear after delivery.

Other diseases have likewise been believed to be due to sex-linked recessive genes, e.g. Leber's optic atrophy. The results of recent investigations suggest, however, that this disease is due to a dominant gene manifesting itself comparatively rarely in females, and that sperm cells carrying this gene are for some reason or other infertile.

In the instances mentioned so far the sex-linkage is complete. The genes are situated in the non-homologous regions of the X-chromosome (see below.) But cases of incomplete sex-linkage are also supposed to exist.

A crossing-over frequency of 1 per cent is called a centimorgan The distance between 2 genes in a chromosome is expressed in centimorgans. A centimorgan is, however, not an absolute linear measure, because identical chromosomes may vary in length from cell to cell

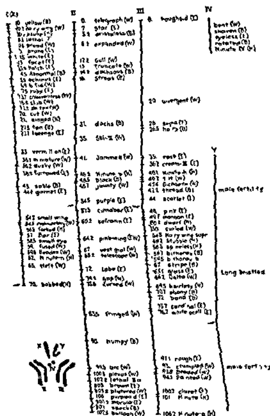


Fig 11 Chromosomes of fruit fly 4 linkage groups plus the Y-chromosome, which, however, carries only few genes The figures denote the gene locus; the letters (after the character) the localisation of the character B: body, E eye, H. hairs, W: wings (from Morgan *et al*)

By calculating the frequency of crossing-over we can find the sites of the genes in the chromosomes. As already stated, the genes belong together in linkage groups The fruit fly, for instance, has 4 groups, corresponding to each of the 4 chromosome pairs, called I, II, III, and IV, where I constitutes the X-chromosome and the others the 3 pairs of autosomes. By calculating the frequencies of crossing-over for 3 genes belonging to the same chromosome

carrying genes are exchanged between the 2 partners of a chromosome pair, whereby the linkage may be abolished.

If we take, for instance, the linked genes A and B, the allelomorphs a and b are likewise linked and carried in the other partner of a chromosome pair. In case of absolute linkage the organism concerned can only develop gametes AB and ab. But if crossing-over takes place at the development of a few of the gametes, with exchange of B and b, for instance, these gametes will have the formulae Ab and aB

By crossing 2 double heterozygotes AaBb ~ AaBb we can in case of absolute linkage only obtain the gametes AB and ab, and the gamete combinations AaBb, AABB, and aabb, which at full dominance will give the phenotypes AB and ab. If crossing-over takes place the 2 hybrids may develop the phenotypes Ab and aB in addition to AB and ab. The frequency of crossing-over can be *calculated from the incidence of these phenotypes*

Crossing-over Frequency. The frequency can, however, be calculated more directly by back-crossing the double heterozygote with the double recessive, if possible.

By crossing

AaBb ~ aabb

the hybrid can, in case of absolute linkage, only form the gametes AB and ab, which gives the 2 gamete combinations AaBb and aabb If crossing-over occurs the double heterozygote can form the gametes Ab and aB as well, and we get the following gamete combinations:

At absolute linkage only	AaBb aabb
At crossing-over also	Aabb aaBb

The crossing-over percentage can be read direct from the incidence of the 2 latter phenotypes, Ab and aB If between them they constitute, for instance, 10 per cent of the offspring from the stated crossbreed, the crossing-over percentage is 10.

Crossing experiments have shown that the frequency of crossing-over is in the main proportional to the distance between the genes in the chromosomes. As it has now furthermore been ascertained that there are many genes in each linkage group, we must conclude that the genes lie linearly arranged, like beads, in the chromosomes This conclusion has been borne out by cytological investigations.

The distance between 2 genes is expressed by the percentage frequency of crossing-over occurring between them

segregating for both characters. Thus, an analysis of linkage between two types is possible in some cases by means of pedigrees Exact information on the parents is often unobtainable. In that case an indirect analysis, by means of siblings taken pairwise, permits a distinction between free recombination and linkage, and an estimate of the crossing-over frequency can thus be made.

Numerous investigations have been made within recent years into linkage in humans It has been shown in several cases that no linkage exists between 2 given genes In other cases the investigations were rather desultory, or of such a tentative nature, that no definite results were achieved. Thus, for instance, characters have been studied whose genetic bases are not quite clear, such as handedness, ability to curl the tongue, warts, mid-digital hairs, character of the external ears, allergic diseases etc. But none of these studies offers a basis for definite conclusions concerning linkage between pairs of traits There is good, almost conclusive, evidence that linkage exists between red hair and the ABO blood group *locus* (Penrose), and between sickling of the erythrocytes (comp p. 245) and the MN locus (Snyder).

The only observation which definitely proves the existence of linkage of genes outside the X-chromosomes in man was made recently in Copenhagen by Jan Mohr (*vide* p 153), who found a highly significant indication of linkage between the Lutheran and the Lewis blood group systems. The two *loci* cannot be completely linked, because two cases of crossing-over have been observed, and because these two groups are apparently independent in a sample from the general population The most likely crossing-over value is found to be about 6 per cent

As previously stated (p 45) we know a number of unquestionably X-borne genes, which, by the nature of the case, must be linked Further, it has been shown that crossing-over may take place between the genes for haemophilia and for partial colour-blindness Pedigrees have been studied in which haemophilia and colour-blindness are transmitted. In one of these families a woman, apparently normal, was a *carrier* of both genes She had 4 sons, of whom the eldest was haemophilic and colour-blind, the second normal with regard to both characters, the third only haemophilic, and the fourth only colour-blind Thus, of the X-chromosomes the woman transmitted to her 4 sons, two were non-cross-overs, while two had crossed over between the loci for haemophilia and colour-blindness. The combined data from all pedigrees known of this type indicate about 10 per cent crossing-over between the loci for haemophilia and colour-blindness.

pair we can determine their sites in relation to each other; e.g., if the frequency between A and B is 10, between A and C 15, and between B and C 5 We can map the positions of a great number of genes in the chromosomes by calculating in this way the crossing-over frequencies between the genes. This has been done to the greatest extent in the fruit fly, but also on a smaller scale in various other animals and plants. The distance of the gene from one end of the chromosome is calculated in centimorgans, and this is called the *locus* of the gene.

2 genes lying rather far from each other in a chromosome show a somewhat lower crossing-over frequency than might have been expected according to the distance. This is due to the fact that double or multiple crossing-over may take place in the chromosome segment between the 2 genes.

2 points of crossing-over never lie very close together, presumably because the chromosomes possess a certain stiffness After a crossing-over break of a chromosome the pieces next to the break are protected against crossing-over. The possibility of renewed crossing-over increases with the distance from the break up to a certain point, where it culminates, indicating that the fragments tend to reach a certain length

A crossing-over frequency of 50 between 2 genes leads to the same process of segregation as at free combination without linkage, being therefore not direct demonstrable.

Linkage and crossing-over of homologous polymeric, complementary or lethal genes may involve particularly complicated conditions of segregation.

The frequency of crossing-over between 2 linked genes does not depend exclusively on the distance between the genes Other factors, such as temperature, age, nutrition, and sex, influence the crossing-over percentage. Crossing-over is often more frequent in females than in males. In *Drosophila* crossing-over in the males (the heterozygous sex) is very rare Similar variations have not been observed in man, but they probably occur

Linkage and Crossing-Over in Man Investigations into linkage and crossing-over among humans are difficult because experimental genetic studies are out of the question and the families relatively small Genes linked so closely that crossing-over never takes place between them, are of course, indistinguishable from allelomorphs

Associations of two characters may have various causes, one of which is linkage If two characters are linked, they are positively correlated in some sibships, negatively correlated in others, corresponding to the coupling- and repulsion-phase of the linkage There is no correlation between the two characters in a sample from the general population *Direct study of linkage is* possible in families with at least one of the parents double-heterozygous and

segregating for both characters Thus, an analysis of linkage between two types is possible in some cases by means of pedigrees Exact information on the parents is often unobtainable. In that case an indirect analysis, by means of siblings taken pairwise, permits a distinction between free recombination and linkage, and an estimate of the crossing-over frequency can thus be made.

Numerous investigations have been made within recent years into linkage in humans It has been shown in several cases that no linkage exists between 2 given genes In other cases the investigations were rather desultory, or of such a tentative nature, that no definite results were achieved. Thus, for instance, characters have been studied whose genetic bases are not quite clear, such as handedness, ability to curl the tongue, warts, mid-digital hairs, character of the external ears, allergic diseases etc But none of these studies offers a basis for definite conclusions concerning linkage between pairs of traits There is good, almost conclusive, evidence that linkage exists between red hair and the ABO blood group locus (Penrose), and between sickling of the erythrocytes (comp p 245) and the MN locus (Snyder).

The only observation which definitely proves the existence of linkage of genes outside the X-chromosomes in man was made recently in Copenhagen by Jan Mohr (*vide* p 153), who found a highly significant indication of linkage between the Lutheran and the Lewis blood group systems. The two loci cannot be completely linked, because two cases of crossing-over have been observed, and because these two groups are apparently independent in a sample from the general population The most likely crossing-over value is found to be about 6 per cent

As previously stated (p 45) we know a number of unquestionably X-borne genes, which, by the nature of the case, must be linked Further, it has been shown that crossing-over may take place between the genes for haemophilia and for partial colour-blindness Pedigrees have been studied in which haemophilia and colour-blindness are transmitted In one of these families a woman, apparently normal, was a carrier of both genes. She had 4 sons, of whom the eldest was haemophilic and colour-blind, the second normal with regard to both characters, the third only haemophilic, and the fourth only colour-blind Thus, of the X-chromosomes the woman transmitted to her 4 sons, two were non-cross-overs, while two had crossed over between the loci for haemophilia and colour-blindness The combined data from all pedigrees known of this type indicate about 10 per cent crossing-over between the loci for haemophilia and colour-blindness

Chapter 6

MULTIFACTOR INHERITANCE. MULTIPLE ALLELOMORPHS — EPISTASY

Complementary Genes. The preceding chapters deal mainly with characters inherited through a single gene or gene pair. Many characters depend, however, on various non-allelic genes. Specific phenotypes occur which develop only when specific genes are present at two or more loci. Such genes, which by interaction produce special phenotypes, are called complementary. The complementary genes resemble the recessive in that 2 interacting genes are required to produce a character, but differ from the recessive by not being allelomorphic.

If, for instance, we have 2 genes, A and B, which in common can produce a certain character, we get the following segregation by crossing of 2 hybrids:

P	AAbb × aaBB
F_1	AaBb
F_2	9 AB — 3 Ab — 3 aB — 1 ab
	7

Thus, we get in the 2nd filial generation 9 individuals with the character, they having both A and B, and 7 without it; in other words, a distribution differing from that for simple Mendelian characters.

Two complementary genes may each have a characteristic effect, but may, when acting in common, produce a new character. This may be instanced by the different forms of comb in fowl. Walnut comb is produced by the joint action of 2 dominant non-allelic genes, one of them alone causing pea comb and the other alone rose comb.

Similarly both normal and pathological traits in man may depend for their development on two or more complementary genes.

Multiple Factors. Characters that depend on a single gene pair are called monomeric. If dependent on a greater number of homologous gene pairs, they are called polymeric (from Greek *meros* = part) or polygenic. This may be called a multifactor inheritance.

When several pairs of genes produce more or less cumulative and uniform effects on a character, they are called multiple factors or homologous polymeric genes.

Some characters are differentiated into relatively few clear-cut qualities. A group of people could without difficulty be separated into those with five fingers on each hand and those with six. Variations in characters of this nature are usually dependent on a single pair of genes

Characters of a more general type, i.e. presented by all members of a race or a species, as for instance height, intellect, build of body, are usually quantitative. Such characters are in many cases dependent on multiple factors.

The genes determining the development of colour in wheat kernels are a classical example of homologous polymeric genes. The wheat kernels may be white or, owing to pigmentation, different shades of red. If a particular sort of wheat has 2 pairs of genes for red kernel colour, R_1 and R_2, in the homozygous form its formula is $R_1R_1R_2R_2$, while the corresponding recessive type with white kernels has the formula $r_1r_1r_2r_2$. By crossing these two varieties the formula for the F_1 hybrid becomes $R_1r_1R_2r_2$, and in the 2nd filial generation we get the following distribution:

$$\underbrace{9\ R_1R_2,\ 3\ R_1r_2,\ 3\ r_1R_2}_{15},\ \text{and}\ 1\ r_1r_2$$

in other words, 15 individuals containing R_1 and/or R_2, thus getting red kernels, while only 1 individual gets white kernels. The greater the number of homologous polymeric genes, the less the segregation taking place. In the presence of 4 homologous polymeric genes only 1 out of 256 F_2 individuals does not have one of these in the dominant form. In the presence of 5 homologous polymeric genes only 1 out of 1024 individuals is recessive for all the genes, and if we have n gene pairs, only 1 out of 2^{2n}

MULTIPLE FACTORS AND VARIATION Characters that depend on multiple factors often vary in degree, each of the homologous genes contributing somewhat to the development of the character on which it acts. The greater the number of dominant homologous genes in a given individual the more pronounced is the character. The colour of wheat kernels may thus vary from white by all shades of red to dark red.

The individuals may then with regard to the character concerned follow the binomial distribution. This may thus depend on multifactor inheritance. A normal distribution may also be caused by environmental agents and by combinations of genetic and environmental factors

If some of the homologous polymeric genes are dominant and others intermediate, a skew frequency distribution may result The same is true, if the interacting genes are not equally and cumulatively effective.

There is no doubt that homologous polymeric factors pla

part in the normal variation. Normal traits are nearly always multifactor. Also in man only *few examples are known of normal traits transmitted* by simple inheritance: the blood group characters, the secretor-non-secretor phenomenon, the ability to taste phenyl-thiocarbamide, and possibly the colour of eyes and hair, and some others. With regard to the blood groups we may even regard group A and B as abnormal in as far as they have formerly developed by mutation from groups O or H (*vide* p. 157).

MULTIPLE FACTORS AND DISEASE. In the cases of hereditary diseases a great many workers have supposed *the mode of transmission to be multifactor*, conditioned by several genes.

Thus, hereditary deaf-mutism has been supposed to be a trihybrid trait produced by one recessive and two dominant factors. In the case of schizophrenia the theory of dimeric recessivity has been advanced; and as for Mongolian idiocy some writers even go the length of presuming that this affection is brought about by five recessive genes, or by two dominant and four recessive genes.

Nowadays, however, the great majority of hereditary diseases are claimed to be monomeric, whereas normal characters are most often to be regarded as polymeric

The normal characters in man are very often graded characters, the inheritance of which is multifactor. Many genes are concerned. Each individual gene produces a small effect, the total result being due to their combined action. When a pathogenetic gene develops by mutation it produces its effect alone, naturally always in relation to the genotypic milieu present in each single individual Gradually the pathogenetic gene becomes counteracted by various factors: natural selection, increased occurrence in the kind in question of modifying genes having an inhibiting or suppressing effect. Soon after its appearance it will manifest itself in the less stable heterozygous form (dominant or intermediate), in later generations only in the more stable homozygous form (recessive). The relations of other genes to the pathogenetic gene is limited to modification or suppression of its effect. An abnormal gene is not very likely to establish a system of interaction with another single gene with great effect, or with two or three other genes. But the pathogenetic gene does not differ fundamentally but only quantitatively, by its greater effect, from the normal Alone it manifests itself plainly, unlike most of the genes producing normal characters, which must be regarded as "weak" when alone.

Multifactor inheritance plays a part in the development of resistance to infectious diseases. In a population that through many generations has been infected with a certain disease the least resistant individuals, who possess only

few of the homologous polymeric genes determining the resistance, will succumb in the course of generations The resistance of the population concerned to this disease will then gradually increase, and the disease will in the course of time become less severe and less widespread in the population.

Predispositions to diseases more or less hereditary must generally be regarded as polymeric. They are graded characters dependent on many genes, which, when appearing alone, have but little effect. This is, for instance the case with regard to the predisposition to tuberculosis, and presumably also to the different bodily (constitutional) types which seem to be correlated to certain mental diseases

It is, however, not quite correct to say that homologous genes act on the same "property", for many properties can on further analysis be differentiated in two or more others The property of resistance to an infectious disease, for instance, is naturally produced by interaction of several different characters. Genes with a resistance-increasing effect are therefore not all homologous polymeric in the proper sense of the term, but no sharp line of distinction can be drawn When we designate normal characters as polymeric this is probably in the last instance due to the fact that we cannot differentiate the individual character into elements which each of them is monomerically determined. The pathogenetic genes differ in principle from the normal only by having a relatively great effect When a pathogenetic gene arises by mutation it naturally acts in common with the other genes, but action in common with another pathogenetic gene is generally easily brough to light by a family investigation

An instance may be mentioned of an experimentally produced morbid condition dependent on 2 genes, a dominant and a recessive.

In one mouse strain anterior pituitary dwarfism occurs as a recessive hereditary condition In another strain adiposity and yellow coat occur as dominant characters. By crossbreeding these 2 strains we can produce individuals with both genes and accordingly with signs of both abnormalities

Crossing of 2 mice heterozygous for dwarfism gives

$$Dd \times Dd = DD + 2\,Dd + dd$$

where d is the recessive gene for dwarfism and D the allelomorph This means ¹/₄ will be dwarfs and ³/₄ unaffected carriers

Crossing of 2 mice with adiposity gives

$$Aa \times Aa = AA + 2\,Aa + aa$$
$$\dagger$$

where a is the dominant gene for adiposity and A the [illegible]

The gene a [illegible]

the animals w [illegible]

life. Of the offspring from two heterozygotes $^{2}/_{3}$ will become adipose, while $^{1}/_{3}$ will be normal.

Crossbreeding of a phenotypically fat mouse Aa with a heterozygote for dwarfism Dd AaDD × AADd gives the following gametes:

AD, aD, and AD, Ad, from which we get the following gamete combinations:

AADD: normal
AaDD: with adiposity
AADd: heterozygous for dwarfism
AaDd: heterozygous for dwarfism with adiposity.

By crossbreeding two heterozygotes for dwarfism with adiposity we get:

AaDd × AaDd, which both may form the following gametes:

AD, Ad, aD, ad, which gives the following gamete combinations:

1 AADD: normal, not heterozygous
2 AADd: unaffected, heterozygous for dwarfism
1 AAdd: dwarf without adiposity
2 AaDD: mice with adiposity, but with no predisposition to dwarfism
4 AaDd: heterozygous for dwarfism with adiposity
2 Aadd dwarfs with adiposity
1 aaDD: not viable
2 aaDd: not viable
1 aadd: not viable

It appears that $^{2}/_{16}$ of the offspring produced by crossbreeding of 2 heterozygotes for dwarfism with adiposity have the formula Aadd. These animals are, in other words, homozygous as regards their predisposition to dwarfism and heterozygous for that to adiposity. They are fat dwarfs.

The dwarfs with adiposity present a new not previously observed multifactor (dimeric) picture. It may be described as a summation of the two original manifestations (*vide* Fig. 12).

The combination of adiposity and dwarfism cannot be regarded as an interaction of two truly complementary genes, because each of them manifests itself plainly when appearing alone. The view that hereditary morbid conditions are conditioned by monomeric genes is probably correct in most cases. Yet we cannot exclude the possibility that more rarely occurring hereditary diseases (syndromes or malformations), chiefly such as occur only in siblings, may develop by the meeting in one individual of multiple factors, each of which has a demonstrable effect.

Neither can we exclude the possibility that within human pathology we may meet with diseases which must be regarded as nosologic entities, but which nevertheless are produced by the interaction of several individually pathogenetic genes. This might be conceived to be the case in such rare diseases as, when occurring familially, are seen generally only in siblings. In the case of Laurence-Moon-Biedl's syndrome, the most important signs of which are mental deficiency, adiposity, hypogenitalism, polydactylism, and retinitis pigmentosa, relatives sometimes present one or a few of the signs belonging to

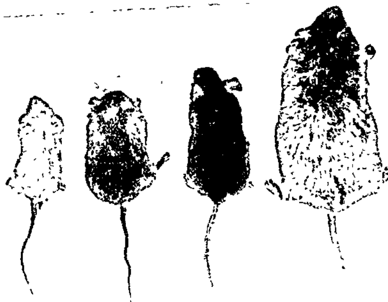


FIG 12 1) Mouse with recessive hereditary anterior pituitary dwarfism Weight 8 5 g Formula AAdd 2) Mouse with recessive hereditary pituitary dwarfism and dominant hereditary adiposity Weight 19 5 g Formula Aadd. 3) Normal mouse, heterozygous for dwarfism. Weight 25.0 g. Formula AADd. 4) Mouse with dominant hereditary adiposity (yellow coat). The gene has a recessive lethal effect. Weight 67 g Formula AaDd

the syndrome, e g polydactylism or the characteristic adiposity. The total complex of signs might be conceived to develop by interaction of non-allelomorphic genes which each produces one or more of the individual signs. The explanation might, however, also be this that the genes for the disease manifest itself differently in the various genotypic milieus present in the different patients.

Characters depending on homologous polymeric genes may show the phenomenon called *transgression*, by which we understand the fact that a certain character may manifest itself in a stronger degree in some of the offspring than in either of the parents A wheat plant, for instance, may present a more intensely red kernel colour than any of the parent plants If each gene adds to the degree of the character a number of individuals in the 2nd filial generation will naturally get the character in a stronger degree than the F_1 individuals

MULTIPLE ALLELOMORPHS It has previously been mentioned that the genes belong together in pairs, occupying 2 parallel loci in 2 homologous chromo-

somes One individual cannot have more than 2 allelomorphic genes But within a species there may very well be found more, which then occur by 2 and 2 in different combinations in the respective individuals. Such genes are called multiple allelomorphs.

The multiple allelomorphs have presumably arisen by repeated mutations from an original homozygous pair of normal genes The mutations have all tended in the same direction, but the result has not been quite the same each time.

The wild type of *Drosophila* has red eyes. But among the strains that have been living through generations in laboratory bottles different mutations have arisen in the course of time with regard to colour of the eyes. Some of these have produced different shades of red eyes, and others white eyes. It has been shown by crossing experiments that the different genes for eye colour really are allelomorphic. In *Drosophila* we know more than 10 allelomorphic genes for eye colour.

Multiple allelomorphs have been observed in a great number of plants and animals. In rabbits, for instance, various allelomorphs are supposed to influence the colour of the coat.

In the case of man numerous instances can likewise be given of certain or likely occurrence of multiple allelomorphism. The blood group characters O, A_1, A_2, A_3 ... and B depend on multiple allelomorphs The same is possibly the case with groups MNS and the Rh subdivisions In this connection it must be borne in mind, however, that we cannot decide whether a system of genes is multiple allelomorphic or closely linked. Other normal characters, e g. the shape and colour of the hairs of the head, are believed to depend on multiple allelomorphs Red and green colour-blindness, varying very considerably in degree, is likewise conceived to be due to several allelomorphs of different strengths, which produce more or less pronounced forms of the abnormality

Other hereditary morbid conditions manifesting themselves in different degrees are presumed to depend on multiple allelomorphs, e g haemophilia and mental deficiency, but nothing certain is known of this fact

Epistasy and Hypostasy. In an allelomorphic gene pair one gene may dominate completely or partially over the other. Two non-allelic genes may behave in a similar way · The action of one gene may cover or suppress that of the other. It is a form of interaction of multiple factors The covering gene is called the epistatic and the covered the hypostatic

Epistasis and hypostasis are well-known phenomena both in plants and animals Where this is present we get a segregation in the 2nd filial genera-

tion differing from that usually expected according to Mendel's laws. If we have 2 dominant genes A and B, of which A is epistatic to B, crossing of 2 hybrids AaBb ~ AaBb will give the following gamete combination in F_2:

$$\underbrace{9\,AB + 3\,Ab}_{12} + 3\,aB + 1\,ab$$

of which 12 have the A character, 3 the B character, and 1 neither of the two characters No certain instances are known of epistasis in human pathology. But in mice, for instance, the grey coat colour, produced by a factor G, is epistatic to the black coat, produced by B, so that the GGBB mouse is grey

Characters depending on recessive, complementary or hypostatic genes may, of course, be transmitted latently through several generations Only if by coincidence the right gene combination occurs in an individual characters which were last seen in a remote ancestor will manifest themselves again This has been believed to be the explanation of the somewhat vague phenomenon called atavism (from Latin *atavus* = ancestor), by which we understand resemblance to remote ancestors.

CHAPTER 7

LETHAL AND SUBLETHAL GENES

By lethal genes we understand genes which, when present in the homozygous form, are deadly. In a living organism they can, of course, exist only in the heterozygous form. The corresponding normal factors are called vital genes

The lethal genes may exert their effect early or late in foetal life, possibly at birth, or in some cases even later This is because there is a gradual transition to sublethal genes which allow survival for a shorter or longer period, generally, however, with reduced viability

Sublethal genes may be dominant The defect they cause will then as a rule occur sporadically in the families, apparently as a non-hereditary abnormality Occasionally, however, such a patient may reach the fertile age and have offspring, where then the dominant inheritance may be observed.

The mouse strain with adiposity, previously mentioned (p 55), is one of the earliest instances known of the existence of lethal genes The fat mice

also have a yellow coat, while the remaining mice of the same strain have a grey coat. By crossbreeding 2 yellow mice we get

$$Gg \times Gg = gg + 2\,Gg + (GG)$$

where G is the gene for yellow colour. But one-quarter of the offspring, GG, die, so we get segregation in the proportion of 1 grey to 2 yellow. In one large survey the crossbreeding was found to be 890 grey to 1783 yellow mice, i e. almost accordance with the expected ratio. But, by examining the uterus of pregnant yellow mice we find that the number of dead embryos almost corresponds to the lacking one-quarter, which have been killed by the double lethal gene. The homozygous yellow mouse embryo develops normally through cleavage and blastocyst formation. Death occurs after the blastocyst has come in contact with the uterine epithelium The embryo disintegrates and is absorbed within 36 hours. Recent experiments have shown, however, that the early death of the homozygous embryos is a result of the uterine environment of the heterozygous yellow mother as well as the hereditary factors inherent in the embryo itself.

The lethal genes then act in such a way that a certain type of gamete combinations cannot be found. If the X-chromosome carries a recessive lethal gene, half of the offspring of the heterozygous sex will die, as such a gene is not checked by a normal allelomorph If X_l is a X-chromosome carrying a lethal gene we get the formula

$$XY \times X_lX = (X_lY) + XY + X_lX + XX$$

If the male sex is the heterozygote the sex ratio is. 2 ○ : 1 □

The lethal gene often has a certain effect even if it is only present in the heterozygous form This is seen in a race of short-legged cattle, the so-called Dexter cattle. By cross-breeding 2 such animals $^2/_3$ of the offspring become short-legged, while $^1/_3$ have legs of normal length Furthermore deformed calves of a chondrodystrophic type, which are not viable, are occasionally conceived and are either aborted or born dead at term in such breeds. The explanation is that, in this race, a gene occurs which in the heterozygous form produces short legs, but in double dose has a lethal effect It is a matter of opinion whether to call this gene dominant or recessive. It is dominant for short-leggedness, but has a recessive lethal effect

Lethal genes have on the whole played a great part in the breeding of domestic animals with its frequent inbreeding. When a bull or another male animal is judged to be a good breeder, it is used for natural or eventually for artificial insemination of a very great number of females, lethal genes will often, as experience has shown, appear in the homozygous form in

the offspring. In cattle many different lethal and sublethal genes have caused birth of bulldog calves, calves with congenital hypotrichosis, or with spontaneous amputations and other deformities. Recessive lethal genes are also known to exist in most other domestic animals, e.g. in horses, where such a gene may cause complete constriction of the colon, and in dogs and in swine. It might be feared that lethal genes would play an increasingly important part, the more inbreeding is employed Nowadays, however, measures are generally taken against these genes by crossing the male breeders with their own offspring in a certain number of cases, to test them before using them for breeding on a larger scale. If no defective offspring results from these crossings, the breeder can safely be used more extensively

In man we find numerous recessive diseases which are so severe that the genes for them may very well be regarded as lethal or sublethal: ichthyosis congenita, myoclonic epilepsy, infantile amaurotic idiocy, tuberous sclerosis, glioma retinae, and many others

Dominant genes with recessive lethal or sublethal effects probably occur in man Certain facts go to show that chondrodystrophy is due to a dominant gene with a recessive lethal effect An instance is known of slight brachydactyly in both partners of a married couple. Of the 3 children born to them one was normal, one typically short-fingered, while the third was a cripple with severe disorders of the whole skeletal system, who died at the age of eleven months This seems to suggest that the gene for brachydactyly is dominant with a recessive sublethal effect Other severe recessive diseases produce effects of a harmless nature in the heterozygous phenotype.

Without having such a radical effect as lethal or sublethal genes hereditary factors may influence the vitality or the viability in varying degrees As regards the viability the genes or the genetic milieu may be neutral, harmful, or beneficial The average duration of life may be used as a criterion of viability Specific genes for longevity hardly exist, but such characters as immunity to infectious diseases and little or no predisposition to cancer or other chronic diseases of course favour longevity, whereas all pathogenetic genes act more or less unfavourably in this respect

A distinction has been made between *zygotic* and *gametic lethal genes* The former have a lethal effect at some time during foetal life or immediately after birth The gametic lethality, on the other hand, affects the sex-cells before fertilisation, gametes of a certain genetic type being infertile. The latter form has not been observed with certainty in man (cf. Leber's optic atrophy, p 230)

Finally, *genes for sterility* occur. These must, of course, be recessive genes transmitted through carriers Certain observations go to show that such steri-

lity genes may also be present in humans; at least families are known in which a strikingly high proportion of its members are sterile.

Chapter 8

MUTATION

Somatic and Gametic Mutation The existence of hereditary variation had been realized long before the idea of mutation took form about the beginning of the present century. But with the introduction of more systematic genetic experiments it became evident that a sudden persisting change of heredity may occur. Such a change is called a mutation (from Latin *muto* = change)

Mutation gives rise to new types, mutants, which are inheritable. New types may, of course, also arise by segregation and recombination As, however, the offspring will develop new combinations, these types will not, remain unchanged through generations New types arising in pure lines can only be due to mutation.

A distinction can be made between somatic and gametic mutation. *Somatic mutation* occurs in the body cells (soma) outside the germ track Hence it asserts itself only in one individual, but is not transmitted by reproduction We know nothing definite as yet about the significance of somatic mutation in man, but the hypothesis has been advanced that it might be the cause of certain intersexual conditions of a *gynandromorphous* character. Further, various workers have advocated the theory that *malignant tumours* may arise through somatic mutation in a single cell which then, through propagation by division gradually forms the tumour tissue

Greater importance is attached to the *gametic mutation,* because it is transmitted through reproduction of the species from one generation to the next Theoretically a gametic mutation may arise at any point of time in the life of the individual, and the earlier it occurs the more gametes will contain the mutating gene. It is generally assumed, however, that the mutations most frequently make their appearance immediately before or during the maturation of the germ cells, and that the mutating gene is present only in a single or very few gametes

Recent years have added considerably to our knowledge of the nature and origin of mutation, especially after Muller in 1927 had demonstrated that mutation could be produced experimentally So the question about mutation

in man became increasingly important and to-day there is no doubt of the frequent occurrence of mutation in man; but it is difficult to form an idea of the frequency.

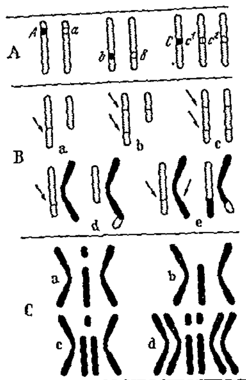


Fig 13 Diagram showing different types of mutation *A*, gene mutation, a, recessive mutation, *B*, dominant mutation, C, c^1, c^2, multiple allelomorphism. *B*, chromosome mutation, a, simple breakage, b, loss of central segment, c, inversion, a segment is twisted round, d, simple translocation, e, double translocation C, genome mutation, a, normal haploid chromosome set, b—c, heteroploidism, $n-1$ and $n+1$ chromosomes, d, polyploidism, 2n chromosomes (After Timoféeff-Ressovsky).

The following forms of mutation may be distinguished:

1) Gene mutation (mutation in the more restricted sense, change of the individual gene).
2) Structural mutations
   a change in the number of the genes (duplication and deficiency mutation),
   b change in the succession of the genes (inversion and translocation).

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pathogenetic gene through mutation. It is also possible that similar clinical syndromes may be due to entirely different genetic changes so that the similarity is only apparent. In the house mouse we know several genetically distinct, but clinically similar syndromes which concern the nervous system.

THE FREQUENCY OF MUTATIONS Different loci mutate at different frequencies The spontaneous mutation rate, i e. the incidence of mutated gametes or chromosomes per generation differs for different mutations, being generally very low (0 0001 to 0 005 per cent) If, for instance, mutation occurs in 1 out of 10,000 gametes, then the mutation rate is 1 in 10,000 or 0 01 per cent. Several unstable genes are known, however, to mutate far more often, some probably at a frequency of about 0 1 per cent. The few mutation frequencies known in man range between 0 01 and 0 001 per cent. The spontaneous mutation frequency seems greater in the old than in the young, not because it depends on the age of the gene, but because a greater number of mutated genes are accumulated in the old germ cells than in the young owing to the longer existence of the former

The mutation rate, the mutation frequency per unit of time, f 1 per generation, depends on the temperature, being raised by higher temperature

INDUCED MUTATIONS Mutations can be produced experimentally, in the first instance by ionizing radiation (α-, β-, and γ-radiation by radioactive substances, X-rays, protons, and neutrons) The only effective non-ionizing radiation is ultraviolet light Furthermore mutations can be elicited by temperature shock and by chemical substances Instances of mutagenic agents are mustard gas, various compounds of nitrogen or sulphuric mustard, and several carcinogens These substances have a special power of penetrating into the cells without killing them

Mutations arise by irradiation only if this hits the chromosomes. Hence they are produced exclusively by rays able to penetrate into the cell. Gametic mutations can be elicited only by rays able to penetrate the tissue surrounding, or covering, the sex-cells The mutations induced by irradiation are essentially the same as those occurring spontaneously However, the frequency of mutation is raised by irradiation The mutation frequency obtained by irradiation is in the main independent of the quality of the latter (in the case of the X-rays independent of wave-length), but dependent on the quantity, being proportional to the dose, to the amount of energy, irrespective of the distribution in time

All these facts suggest that mutation is due to a so-called elementary pro-

3) Chromosome mutations
   a. change in the number of individual chromosomes ($2n \pm 1$, $2n \pm 2$, etc.),
   b. change in the number of chromosome sets (haploids and triploids, etc).

These forms of mutation are, however, most frequently collected in one. In practice it may be difficult to distinguish between the different types of mutation. In most cases the hereditary change of phenotype is the only change observed. In Drosophila and some plants cytological changes can be seen parallel to phenotypic mutation

The two partners of a pair of genes mutate independently, just as different genes do More than one change may occur in a given gene from different individuals, producing multiple allelomorphs.

The mutations may be both recessive, intermediate, and dominant. The gene mutations are believed as a rule to be recessive, while the structural mutations often are dominant.

It is the prevailing view that the recessive mutations are the most frequent. Presumably, however, several mutations are intermediate, and the theory has been advanced that the favourable intermediate mutations gradually develop through the generations to become dominant, whereas the pathological gradually become recessive.

Evolution is assumed to have a tendency to establish complete dominance of the normal type in relation to the pathological type arising from mutation, which reduces the viability of the individual.

In some individuals the pathogenetic gene has relatively little effect. This is due to the fact that these individuals have genes which display no marked expression *per se,* but have a modifying effect on the mutation The individuals with the greatest number of modifying genes of this kind do best The modifiers therefore gradually spread in the population, thereby changing the mutation more and more towards recessivity. The possibility has also been suggested, however, that not the modifying genes, but the normal allelomorphs gradually are selected until they dominate completely over the mutated gene.

The same disease may be seen to occur in different forms, when arising by mutation in a population Sometimes it is entirely recessive, and sometimes more or less intermediate or dominant. Some investigators hold that this applies to many hereditary diseases, which then present the so-called "conditioned dominance" Such hereditary diseases are thus able to appear sometimes in the dominant or intermediate form and sometimes in the recessive form, depending on the time that has elapsed since the occurrence of the

Soon after the theory of mutation had been advanced by de Vries at the beginning of the present century the question naturally arose whether mutation occurs in man, too In 1907 Apert advanced the view that congenital anomalies and malformations, such as *dislocation of the hip, chondrodystrophy*, and *cleidocranial dysostosis* should be looked upon as being due to mutations Many other students of heredity likewise believe that hereditary diseases in man not infrequently arise through mutation.

Within recent years attention has been called to the danger which "our load of mutations" involves for the human race, and different forms of genetic death have been mentioned Pathological mutations are important causes of disease. Very little has been done so far to prevent and restrict the diseases due to mutation This is a field within which further studies are greatly needed

In the case of man, where relatively few generations only can be traced, and where crossbreeding experiments cannot be made, we shall, of course, never be able to demonstrate with certainty that a recessive autosomal disease has arisen by mutation

Still, certain observations seem to suggest that recessive pathological mutations not infrequently occur in man Hanhart has made studies in remote mountainous districts in Switzerland where the population is very isolated and has little contact with the outside world, and where furthermore confessional motives contribute to inbreeding. Here he observed, for instance, 31 cases of *recessive hereditary dwarfism*, which he thinks arose in 6 different foci in different cantons Similar observations were made concerning recessive hereditary deafmutism. These genes therefore probably have a relatively high mutation rate

Sex-linked recessive pathological characters can be shown with greater certainty to have arisen through mutation

Observations regarding dominant diseases make it reasonable to assume that these also occasionally arise through mutation. If thus a disease which is known from experience to be due to a dominant gene suddenly appears in a previously healthy family and afterwards is inherited with regular dominance, the disease has probably arisen through mutation in one of the parents of the individual who is the first to display the disease in the family concerned Mohr and Wriedt have described a family with the typical dominant trait of *brachyphalangia* The data of the progenitors, who lived about the middle of the eighteenth century, could be procured None of these had brachyphalangia. This malformation first appeared in their daughter, from whom it was inherited as a typical dominant trait.

Hanhart has described a Swiss family with brachyphalangia of the index

cess. If we take the gene to be a large complex organic molecule, we must suppose mutation to be due to a single ionisation within a specific volume "the target", which provides the necessary energy for molecular transformation. This causes a rearrangement of the atoms of the molecules, giving rise to a gene mutation or chromosomal break The probability of hitting the target is proportional to the radiation dose. There is no threshold for irradiation below which point mutation should not be produced.

The mutations are discontinuous processes comparable to quantum transition. Some mutations are reversible.

THE CAUSE OF SPONTANEOUS MUTATIONS. Spontaneous mutations have been believed in the past to be produced exclusively by the ionizing radiation always present in the form of natural earth radiation and cosmic rays. This can hardly be correct It has been calculated that the dose received through this radiation can produce only a small proportion of the spontaneous mutations occurring in the fruit fly, whose gametes mature within a few weeks of the formation of the individual. The majority of the mutations in this animal must therefore be supposed to have other causes Chemicals produced within the organism may be mutagenic Compounds produced by normal cellular metabolism and natural fluctuations of energy may presumably cause mutation Genes at one locus may increase the mutability at some other loci through chemical action

Many genes exert a different effect when placed in a new chromosomal neighbourhood. The rearrangement of genic positions, e g after inversion of a chromosome segment, may lead to a new inherited phenotypic effect It is a position effect, possibly caused by chemical products, but different from mutation.

In human gametes the mutations may accumulate during 20 to 50 years. The total quantity of natural irradiation received by human gametes per generation is perhaps sufficient to cause an essential proportion of natural human mutations; but many of these mutations are most likely due to endogenous chemical mutagens or random energy fluctuations

MUTATION AS A CAUSE OF DISEASE. In their efforts to investigate the aetiology and pathogenesis of the various diseases pathologists must continually seek new paths. Within the past few centuries, during which time pathology has undergone a considerable development, the causes of many diseases have been discovered, chiefly by the aid of morbid anatomy, physiology, bacteriology, parasitology, and experimental pathology The significance of mutation has only recently been fully realized.

back-crossing with double recessive genes. Hence it is hardly possible to determine the frequencies of mutation for recessive genes in man. With dominant and sex-linked traits it is different.

Taking for granted that the disease occurs at an approximately constant frequency through a succession of generations, and knowing, too, that the

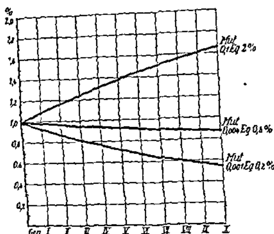


FIG 14. The effect of mutation and selection for a recessive disease in a random mating population during 10 generations Initial frequency of the disease 1 % Negative selection 50 % Mutation rates 0 1, 0 004 and 0 001 (theoretical, very high values) Equilibrium will be attained at frequencies of 2 per cent, 0 8 per cent and 0,2 per cent respectively, in the first of the 3 examples comparatively quickly, in the second case more slowly, and in the third very late (From von Hofsten, *Hereditas*, p 256, 1951).

disease reduces the fertility of the individual suffering from it, we may conclude that a certain frequency of occurrence must be due to mutation. If the disease depended exclusively on hereditary factors it would soon become extinct, because of the reduced fertility of the patients.

Hereditary diseases interfere with the prospects of reproduction of a human being The early death of affected individuals limits the prospects of marriage Sterility and reduced numbers of children are factors which between them cause an impaired reproductive fitness leading to decreased frequencies of the pathogenetic genes from one generation to the next. If the fitness is, say, ½, ten generations would cause a reduction of the abnormal gene to $(½)^{10}$ or less than 0 1 per cent of the original frequency. A nearly normal reproductive fitness, reduced by only 1/10, would during 10 generations give a fall to $(9/10)^{10}$, or less than 4 per cent, of the original frequency

finger. Here, too, the data of the ancestors were said to be reliable as far back as the first instance of this malformation in the family, about two hundred years ago, and the progenitors were stated both to have been normal. It seems as if the same dominant mutation, producing quite identical characteristic malformations, has taken place about the same time in Switzerland and Norway, as there is no evidence to suggest that the two families could be related. We must admit, however, that it may be doubtful whether we can absolutely rely on data concerning the members of a family born in the 18th century.

Another dominant lesion which may reasonably be assumed frequently to arise by mutation is *hereditary keratosis,* appearing as abnormal cornification of palms and soles. Over 50 such families have been described in which the lesion appeared as a typically dominant abnormality, distributed all over the world in all races. No relationship could be demonstrated between these families, and no other reasonable explanation of this phenomenon can be offered than that the abnormality has arisen again and again through mutation. The mutation frequency at this locus, in other words, appears to be high The corresponding normal gene must be relatively unstable and tend to mutate *in a certain way, since the clinical entity concerned is extraordinarily* constant and shows regular inheritance.

Another dominant lesion manifesting itself completely, known all over the world, is *Huntington's chorea.* In America, Davenport has described 4 large families comprising 962 cases These families are traceable to the 17th century. and no interrelationship is demonstrable In another investigation of this affection, again carried out in the United States, all the cases comprised could be traced to 3 *married couples who emigrated from England in 1630,* i e. more than 3 hundred years ago. Reports have also come from other countries in which choreal families could be traced up to 10 generations back. In Sweden Sjögren has studied 88 cases in two parishes in Northern Sweden, which could all be traced back to 5 progenitors. In Germany, Switzerland, and Denmark several choreal families mutually independent have been investigated. As this disease is so markedly dominant and never skips a generation it is only reasonable to presume that *it, too, often arises through mutation*

Many other observations argue in favour of the view that hereditary diseases may arise through mutation; but this has only recently been proved We are now able to calculate the frequencies of mutation or the mutation rates for various hereditary diseases

THE MUTATION RATES OF DISEASES The mutation rates of recessive autosomal genes can be *determined only in the presence of inbreeding or extreme*

Mørch has calculated the mutation rate for *chondrodystrophy*. The disease is dominant, and the reproductive fitness of the patients is markedly reduced.

The mutation rate has been calculated direct as follows: Out of 94075 children born at term in the Lying-in Hospital, Copenhagen, 10 were chondrodystrophic. In 2 cases the disease was inherited from one of the parents, while in the others it had probably arisen by mutation. The mutation must have taken place in one of the parents in the 94073 marriages (or other connections). This gives a mutation rate of $\frac{8}{94073}$ = 0.000085 per individual per generation and 0.000042 per chromosome per generation. It was further stated that 108 chondrodystrophics had had a total of 27 children, which gives a fertility rate of $\frac{27}{108}$ = 0.25. As only about half of the children are chondrodystrophic, the fertility with regard to chondrodystrophy is 0.125. The 108 chondrodystrophics have had altogether 457 non-chondrodystrophic brothers and sisters, and these siblings had a total of 582 children. The fertility of the siblings is thus $\frac{582}{457}$ = 1.2735. The proportion of the fertility of chondrodystrophics to that of non-chondrodystrophics is thus $\frac{0.1250}{1.2735}$ = 0.098 = f.

The value for f, the fitness or effective fertility, will naturally always be difficult to calculate *quite accurately*. The method here employed, namely the comparison of the fertility of the patients and their unaffected siblings, is also subject to errors.

As stated above, the frequency of the disease in the population at birth, x, is $\frac{10}{94075}$. In each generation the gene disappears in $(1-f)x$N cases (N = *population*). If the disease keeps a constant frequency, these genes must be replaced by mutation. For this disease, then, the mutation rate per chromosome per generation is

$$\frac{(1-f)x\mathrm{N}}{2\mathrm{N}} = \tfrac{1}{2}(1-f)x = \tfrac{1}{2}(1-0.098)\ \frac{10}{94075} = 0.000048.$$

Thus, the mutation rate calculated indirectly is in close agreement with that determined directly, which was 0.000042 or about 4×10^{-5}. If some chondrodystrophic zygotes are eliminated before birth, the mutation rate is higher than that calculated here.

Andreassen found a total of 81 haemophiliacs among the 1820000 males in Denmark in 1943. The average lifetime of haemophiliacs is approximately

It may be possible to estimate the mutation rate when the hereditary disease in question is rare and reduces the reproductive fitness so much that selection and mutation approximately balance one another. The gene need not necessarily be fully penetrant.

Haldane made the following calculation for *haemophilia,* which is a recessive sex-linked disease: Haemophilia occurs at present in the English population at a certain frequency, and we know that it markedly reduces the fertility of the patients concerned. If haemophilia did not arise through mutation all men in England should have been affected at the time of William the Conqueror. As this was hardly the case the disease must in a certain number of cases be due to mutation Selection is kept in balance by mutation

If the population is in equilibrium, as many genes are destroyed by selection as are produced by mutation in each generation An equilibrium exists between loss and gain. The rate of mutation must have balanced the rate of loss.

If x is the frequency of haemophilic males, f the effective fertility of these males, and 2N the number of individuals in the population, then $(1-f)xN$ haemophilic genes will disappear in each generation. This number must then be replaced by mutation if we reckon that the frequency of haemophilia remains relatively unchanged from generation to generation. As, however, each of the N females in this population has 2 X-chromosomes in her gametes, while each of the N males has only 1, the average mutation per X-chromosome in each generation will be $1/3 \times (1-f)x$, or, if f is low, a little less than $1/3\ x$, Knowing the frequency of haemophilia in males and being able to calculate the fertility of the haemophilic males we may be able to determine the mutation rate

Similarly the mutation rate of a rare dominant gene, which is able to keep the frequency of the disease unchanged in the population can be calculated to be $(1-f)x$; for in a population of 2 N individuals $2N\ (1-f)x$ genes will disappear in each generation. The mutation rate per individual per generation is then $(1-f)x$ Per chromosome per generation it is $1/2(1-f)x$.

In other words, if we are able to determine the frequency of a dominant or sex-linked recessive disease in a population and the fertility of the respective patients, we are also able to calculate the mutation rate for the disease, provided the frequency of the disease is fairly constant from generation to generation.

Determinations of the values for f and x may be relatively difficult and give only a fair degree of certainty. Within recent years these determinations have nevertheless been tried for several hereditary diseases, the mutation rates of which have thus been calculated approximately.

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18 years, i.e. about one-third of that of normal males If the lifetime of haemophiliacs had been normal the frequency of haemophilia would have been

$$x = \frac{81 \times 3}{1820000} = 0\ 000133$$

If we estimate the reproductive fitness of haemophiliacs, *f*, at about 0.3, the mutation rate for haemophilia lies between 1 :20000 and 1 :50000 per chromosome per generation, *viz*

$$1/3(1-0\ 3) \times 0\ 000133 = \text{about } 3 \times 10^{-5}$$

Some cases of haemophilia, especially the sporadic cases, have, however, undoubtedly avoided observation; for that reason the mutation rate is higher than calculated above.

Similar investigations have been made with regard to other dominant affections. Møllenbach, for instance, has studied this aspects of *anridia*, which manifests itself by complete absence of the iris and is accompanied by a very marked impairment of vision On the basis of his observations in Denmark he estimates the mutation rate of this affection at between 1 ·50000 and 1 : 100000, at least more than 10^{-5}.

The mutation rates of a few other diseases have been roughly estimated and have been found to be 10^{-4}-10^{-6}, for instance, for retinoblastoma 1.4×10^{-5} and for tuberous sclerosis $4\text{-}8 \times 10^{-6}$ (comp p 265)

The rates here reported are those of particularly mutable human genes. They are higher per generation than those of the most mutable normal genes in *Drosophila* But the daily rates are much higher in *Drosophila* than in man. If the radiosensitivity of human genes is about the same as in *Drosophila* natural radiation may account for almost all human sublethal mutations

Thus it is evident that hereditary affections often arise by mutation This fact obviously is of great importance. Investigation into the inheritance of a given disease is incorrect unless we know, or at least have some idea of how often it arises through mutation Any genetic analysis of a population is unfeasible without a knowledge of the mutative changes taking place in it It is hardly possible to evaluate the significance of eugenic measures, such as sterilisation, etc, if we do not know whether the diseases concerned continue to appear through mutation, and if so, how often

It will therefore be important in future to investigate the significance of mutation as a cause of disease This is a difficult task, however, which can be carried through only if we have a thorough knowledge of the frequency of the disease, its inheritance, and the reproductive fitness of the patients suf-

fering from it, and if we are able to follow and control the behaviour of these diseases down through the ages.

Such a thorough knowledge concerning the hereditary diseases can be obtained only where special institutions are ready to work with this problem. A thorough medico-genetic or eugenic registration must be established in the various countries, comprising all important hereditary diseases, and this registration must, of course, be kept up to date.

Only by international collaboration will it be possible gradually to elucidate the part played by mutation as a cause of disease.

ARTIFICIALLY INDUCED MUTATIONS IN MAN. There is no doubt that X-rays and radium may produce mutation in man. Patients treated by X-rays or radium, as well as the staffs of X-ray clinics and X-ray technicians are exposed to such irradiation; further, all who work with radioactive substances or in uranium mines or with atomic energy. Finally, the military use of the atomic bomb and radioactive substances may involve exposure to irradiation of a great number of people

We must distinguish between physiological and genetic effect of the irradiation

The physiological effects are such as haematological changes and burns of the skin and other tissues, and cataracts. Following irradiation somatic mutations may probably arise, which may be responsible for the slow healing of X-ray burns or the complete lack of it, and which perhaps also have a carcinogenic effect Physiological action is not accumulated in the same way as genetic Minor burns and haematological changes are not irreparable, and they are less readily produced by a certain dose, if this is given in fractions rather than if it is given all at once

The upper tolerance dose for physiological effects is reckoned to be 0 1 r (roentgen) per day The whole body of an individual can be exposed to a dose of this magnitude daily over a long period without producing burns or changes of the blood cells Continued irradiation with 0 1 r per day may, on the other hand, have some genetic effect owing to the accumulation.

Gametic mutation is, of course, particularly to be feared in X-rays of or close to the gonads Previously temporary sterilisation of women was occasionally performed by X-rays on the ovaries, particularly in cases of refractory metrorrhagia This method of treatment has now been abandoned for fear of eliciting a gametic mutation in the patient, which might manifest itself in possible offspring If the irradiation has given rise to dominant mutations, they will manifest themselves in the next generation Sex-linked mutations will also generally manifest themselves in the first, or the imme-

18 years, i.e. about one-third of that of normal males. If the lifetime of haemophiliacs had been normal the frequency of haemophilia would have been

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to new mutations, then this will mean about 1000 out of 100,000 newborn infants will have such defects, which must either be dominant or X-linked recessive. In other words, the number of damaged among the newborn has increased by 800, from 200 to 1000 To these may be added the recessive mutations which do not manifest themselves until the more or less remote descendants This is a problem of great social importance.

Various calculations have been attempted of the number of mutations that may be conceived to occur following radioactive warfare, e g. following an atomic bomb explosion, contamination of large areas by radioactive substances, or other cunning military methods. Experience is, however, as yet very limited within this field But the number of severe gametic mutations due to this irradiation is believed to be relatively limited, as the interval between the dose having a marked mutagenic action and that having a sterilizing or killing dose is comparatively small It has been estimated that individuals receiving a total body irradiation of about 450 r or more from explosive radiation are killed Among the survivors after an atomic bomb explosion there will no doubt occur a somewhat increased number of dominant abnormalities as well as several recessive lethal allelomorphs, which will manifest themselves in future generations, but the transmissible genetic consequences of an atomic bomb are probably small as compared to the *immediate effect*.

Anyway the gametic mutations due to artificial irradiation involve great danger of development of hereditary diseases and defects in the descendants of the irradiated individuals through innumerable generations. For the sakes of future generations everything possible ought to be done to protect humans from mutagenic irradiation

Chapter 9

INBREEDING, INTERMARRIAGE, AND CONSANGUINITY

Inbreeding By inbreeding we understand the mating of closely related individuals

Characteristic features of inbreeding or intermarriage are the increased *homozygosity* and the *loss of ancestors* The number of ancestors is reduced in proportion to the degree of inbreeding

We get the best impression of how inbreeding increases the homozygosity

diately following generations, if transmitted at all. Recessive mutations, on the other hand, are not demonstrable till later, in man not before the third generation after its occurrence, and then only in cases of consanguinity; otherwise still later—perhaps even hundreds or thousands of years after its first occurrence

This is probably one of the reasons why gametic mutations known for certain to have been artificially induced have not yet been observed in man. There is, however, no reason to doubt their existence.

X-ray radiation should therefore as far as possible be avoided on or close to the sexual glands of patients who have a chance of bearing children Irradiation of the uterus during the first 3 months of pregnancy should likewise be foreborne, as such is known by experience sometimes to cause malformations in the embryo. Patients, workers, and others exposed to irradiation ought in the general to be protected in every possible way.

Irradiation may in the gonads cause elimination of the germ stem cells prior to meiosis, relative sterility or semisterility, or early death of gametes or developing zygotes. The various cells differ considerably in radiosensitivity. Tissues in which many cell divisions occur are generally very radiosensitive. The sensitivity of the cells varies at different stages of the mitotic cycle These facts naturally complicate all calculations of the mutagenic effect of irradiation.

An attempt has been made to estimate the damage which gametic mutation due to irradiation may cause.

It has been roughly estimated that 100 r applied to each of 1,000,000 gametes causes one gamete to undergo a mutation corresponding to a specific locus. If we take it that man has about 25,000 gene pairs, this means that out of 1 million gametes irradiated by 100 r about 40 are mutated

On the basis of experience from experiments, with fruit flies and mice, among others, an attempt has been made to estimate the X-ray dose required for doubling or tripling of the natural mutation rate. This dose is presumably about 200 r in the case of man.

The natural mutation rate in man, or the incidence of abnormalities due to new mutations, is probably not over 1 or 2 in 1000 births Let us reckon it at 0.2 per cent. If this incidence is multiplied by 5 by irradiation with 800 r the risk of a hereditary defect in the offspring of a person whose germ cells have been exposed to this dose will rise from 0.2 to 1 per cent, but 99 per cent of the children will remain normal. This dose thus has no fatal effect for the individual person. The conditions are different where a whole group of a population is concerned, all exposed to irradiation If the irradiation dose quintuples the number of children with congenital defects due

we may contribute to the furthering of some particularly desirable properties. It is, of course, useless to select individuals on the basis of variation caused by differences in environment. Phenotypic selection may give some improvement, but will on the whole result in many individual failures. As for domestic animals the intense inbreeding involves, however, as previously stated, a risk

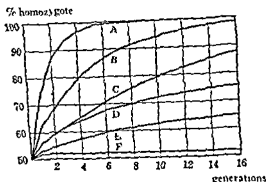


FIG 15 The percentage of homozygosity for one pair of allelomorphs in successive generations under various systems of inbreeding A self-fertilisation; B brother-sister matings, C double first cousins, D half-brothers and -sisters, E single first cousins; F, second cousins (After Wright)

of manifestation of lethal genes Hence individuals are often only selected for breeding if they produce offspring of the desired type (progeny selection).

Regarding improvement of plants, e g the ordinary cereals, experience has shown that *inbreeding depression* often occurs, particularly in cases of self-fertilisation of such plants as rye, which normally are cross-fertilisers. After a certain rather short period of inbreeding the offspring show a considerably lower total height and vitality than the starting material The depression will often in the course of some generations (4 to 9) reach a certain minimum, which is frequently called inbreeding minimum Crossing now with another inbred or non-inbred line removes the inbreeding depression.

Similar conditions have not been observed in ordinary experimental animals, but, of course, self-fertilisation is not possible here. The same rat or mouse strain has for many years been inbred in the manner that only brother and sister have been mated In some cases this has been done through more than 25 generations without deterioration of the strain. In other cases the fertility of the animals proved to decrease or the young would die immediately after birth from no demonstrable cause But, as a rule, inbreeding may be continued for a very long time, when it is combined with selection, without

by studying the most rigorous form of inbreeding, self-fertilisation. If we take a single individual Aa, it will by self-fertilisation produce the offspring

1 AA : 2 Aa : 1 aa, i e. 50 per cent homozygotes.

By continued inbreeding we get the following distribution in the next generations, if we reckon with 4 offspring individuals from each individual:

$$\underbrace{4\,AA \quad 2\,AA}_{6\,AA} \,.\, \underset{4\,Aa}{4\,Aa} \,.\, \underbrace{2\,aa \quad 4\,aa}_{6\,aa} = 75 \text{ per cent homozygotes}$$

$$\underbrace{24\,AA \quad 4\,AA}_{28\,AA} \; \underset{8\,Aa}{8\,Aa} \,.\, \underbrace{4\,aa \quad 24\,aa}_{28\,aa} = 87\ 5 \text{ per cent homozygotes}$$

By this intense form of inbreeding we find, in other words, 50 per cent homozygotes in the 1st generation, 75 per cent homozygotes and 25 per cent heterozygotes in the 2nd, 87 5 per cent homozygotes in the 3rd, and by proceeding in this way we find

93 75 per cent homozygotes and 6 25 per cent heterozygotes in the 4th generation,
96 875 per cent homozygotes and 3 125 per cent heterozygotes in the 5th generation,
etc.

In each generation the number of heterozygotes is reduced by 50 per cent The homozygosity will be practically complete in the course of a comparatively few generations Similarly, by complete inbreeding starting from an individual that is heterozygous for 2 gene pairs AaBb we get in the next generation $(50\,\%)^2 = 25$ per cent homozygous for both gene pairs, in the following $(75\,\%)^2 = 56\ 25$ per cent, etc Correspondingly, n-double heterozygosity gives in the 1st generation $(50\,\%)^n$ homozygotes, in the 2nd $(75\,\%)^n$, etc. Linkage further complicates the conditions Homozygosity for a very great number of genes is thus quickly obtained by such a rigorous inbreeding as the one which can be carried through by self-fertilisation But even in case of less intense inbreeding the homozygosity increases, though more slowly, as appears from Fig 15

Inbreeding has therefore been extensively used for improvements of plants and domestic animals, where valuable results are achieved when the inbreeding is combined with a suitable selection We distinguish between natural selection and artificial selection While artificial selection is of decisive importance for breeding of animals and plants, it generally plays no part in the case of humans.

By inbreeding we get a homogeneous race, and through suitable selection

plainly show a decrease in the frequency of such marriages. In Bavaria, for instance, the incidence of cousin marriages was 1876-80: 0.87 per cent (188,973 marriages) and 1926-33: 0.20 per cent (474,268 marriages). In England 0.61 per cent of the parents of 49,315 adult in-patients in general hospitals 1880-1925 were first cousins, while among 10,236 children admitted 1925-39 to general hospitals 0.40 per cent had been born of first cousin parents.

Numerous statistics are available of the frequencies of consanguineous marriages in different countries and different parts of a country. These show great variations. The frequency of first-cousin marriages is generally slightly lower than the total frequency of other consanguineous unions, up to and including second cousins. Reliable figures are, however, difficult to obtain on this point. In Western Europe the incidence is probably to-day on an average about 0.5 (0.1 to 1.0) per cent for first-cousin marriages.

In the large statistical calculations the figures are no doubt too low, because the conjugal partners have not been questioned with sufficient care. A minor, more thorough investigation in Denmark (1941) showed 1.2 per cent first-cousin unions and a total of 2.1 per cent consanguineous marriages among

[illegible]

owing to its geographical condition and local customs, we may mention the Fiji Islands, where during 1850-95 out of 448 marriages in 12 villages 29.7 per cent were first-cousin marriages. At Obermatt in Switzerland 11.5 per cent of 52 marriages were found to be between first cousins, and 53.8 per cent consanguineous marriages up to and including second cousins. In 3 northern Swedish parishes there were 1880-1945 found 1.0, 2.9, and 6.8 per cent first-cousin marriages, and on a small rural island 1850-1920 3.0 per cent.

In the Netherlands the population in the southern provinces is chiefly urban, and there are many Catholics. In the northern provinces, on the other hand, the population is mainly rural, and practically all are protestants. 1907-16 the percentage of intermarriage was about 0.3 in the southern provinces and about 1.0 in the northern. 1937-46 the corresponding percentage figures were about 0.10 and 0.2-0.3 respectively, counting intermarriage up to and including the 4th degree. The average incidence of consanguinity for the whole country was 0.7 per cent 1907-16 and 0.169 per cent 1937-46. The figures accord well with Polman's observation that heredit[illegible]

cul[illegible]

in

the

[illegible] of consanguinity, the break-up of isolates, the higher percentage of intermarriage in urban than in rural districts, and the dependence of intermarriage on religion and custom.

degeneration being demonstrable. After many years of inbreeding the animals of such a strain have become very much alike. They have the same appearance and respond alike to environmental influences. Such a strain is therefore particularly fit for experiments, biological titrations, and the like. If the progenitors of a strain carry latent genes for diseases or abnormalities, these will, however, naturally manifest themselves by inbreeding.

INTERMARRIAGE. In humans intense inbreeding is generally out of the question In most countries, e.g. in Western Europe, marriage between near relations is prohibited One is not allowed to marry relatives in the direct ascending or descending line, nor siblings, and a special licence is required to marry a step-parent or a step-child. In several places, e.g. in parts of the U S A., marriages between niece and uncle, nephew and aunt, and between first cousins are also prohibited. In some countries even unions of second cousins and other more distant relations are illegal Among Catholics first cousins are not allowed to marry without special dispensation. These provisions are in the first instance rooted in general moral and religious ideas that sexual union of closely related persons is something objectionable, but are probably also based on observations regarding the progeny of consanguineous marriages.

Marriage between more distant relations is not prohibited, and such marriages are not infrequent. Intermarriage may be due to geographical conditions or have social or traditional causes On small islands, in narrow valleys, or in other remote districts inhabited by a limited number of families having only little communication with the outside world an ever increasing degree of intermarriage cannot be avoided In such an isolated place the population will finally constitute one large family

FREQUENCIES OF CONSANGUINITY IN VARIOUS POPULATIONS No definite frequency figure can be stated for consanguineous marriages It varies from time to time and from place to place During the past hundred years or so there has been a steady decrease in the frequency of such marriages. The causes are various Intercommunication has become much easier, migrations are taking place on a large scale, not only from one country to the other, but also from country to town Isolates gradually cease to exist, as do also social and racial lines of distinction.

Furthermore, the families have become smaller, and thus the probability of near-relative marriages has decreased Several calculations are available from various countries of the incidence of consanguineous marriages from the latter half of the preceding and the present century respectively which

TABLE 1

The incidence of consanguinity in the parentage of individuals with certain recessive diseases.

(After Neel, Kodani, Brewer, Anderson, Amer. J. Hum. Gen. 156, 1, 1949).

Trait	Incidence of first cousin marriages among parents	
Albinism	European	18-24 per cent
	Japanese	37-59 „ „
Infantile amaurotic idiocy	European	27-53 „ „
	Japanese	55-85 „ „
Ichthyosis congenita	European	30-40 „ „
	Japanese	67-93 „ „
Total colour-blindness	European	11-21 „ „
	Japanese	39-51 „ „
Xeroderma pigmentosum	European	20-26 „ „
	Japanese	37-43 „ „

The frequency of a recessive gene, q, in a population may be calculated if the proportion of first-cousin marriages in the population, c, and among the parents of affected individuals, k, is known Various formulae for this purpose have been suggested, e g the following by Weinberg and Dahlberg:

$$q = c(1 - k) \quad (16k - 15c - ck)$$

By means of this formula the frequency of the recessive gene, q, has been calculated for the diseases mentioned in Table 1. For amaurotic idiocy q was found to be 0 0006 to 0 0018 in Europe, for ichthyosis congenita 0.0010 to 0 0015, and for total colour-blindness 0.0025 to 0 0055 The results achieved by means of this formula must, however, be accepted with considerable reservation It presupposes, among others, that the population concerned is in a state of panmixia, which a human population hardly ever is Formulae have also been found for calculating the sizes of the "isolates" into which a population is subdivided on the basis of the frequency of cousin marriages. But these formulae likewise presuppose that cousin marriages are contracted at random, and thus are for this reason, among others, of only limited value.

Where more common recessive diseases are concerned, for which the gene is relatively frequent in the population, the accumulated occurrence due to intermarriage is far less pronounced.

In addition to intermarriage for the reasons mentioned above, this may also be seen in families which for other special reasons are closely attached to each other, e g in princely and noble families, financial and manorial dynasties, and the like A historic-genealogical investigation revealed that all

Recently (1948-9) an important investigation was made by the Atomic Bomb Casualty Commission in Hiroshima, Kure, and Nagasaki (Neel and others) into the consanguineous matings in Japan. It was found that among about 24,000 marriages approximately 4 per cent were first-cousin marriages, a much higher percentage than in any European urban population.

CONSANGUINITY AND DISEASE. In the general intermarriage probably involves no risk as long as it takes place in thoroughly normal families. Degeneration in the sense that the families deteriorate because of intermarriage or, as it is also said, because they do not get sufficient fresh blood from without, can hardly be said to occur. Intermarriage does not create weakness or defects, it brings them to light.

This view is borne out by the experience, fairly often gained, in cases of extreme intermarriage in human families. In the Ancient Egyptian royal families marriages between siblings through several generations were not infrequent, without this leading to any particular degeneration Brother-sister unions were also common in the Incas Dynasty, where such are said to have taken place through 14 generations with no demonstrable deteriorating consequences.

The same cannot be said to apply to consanguineous marriages in families where recessive, complementary or hypostatic diseases occur, which may be transmitted through several generations without being discovered If 2 unaffected carriers marry there is a risk that some of the children may get the disease concerned.

Many instances may be mentioned of this phenomenon

That deaf-mutism occurs particularly in families with a high degree of intermarriage was already ascertained in the 19th century. Many consanguineous marriages also occur in families with myoclonic epilepsy, the first disease for which recessive inheritance was demonstrated Gradually it was realized that the incidence of consanguinity is high among parents of patients with rare recessive diseases, higher the rarer the recessive disease These facts were recently studied by the above-mentioned Atomic Bomb Casualty Commission, which invstigated 5 rare recessive diseases in the previously mentioned Japanese districts and compared the results with those from earlier investigations by various workers in Europe.

The result appears from Table 1

Intermarriage being more frequent in Japan than in Europe the incidence of intermarriage among the parents of these patients is also higher in Japan than in Europe. The frequency of intermarriage is seen to be greatly increased, to 10-20 per cent at least, and in some cases to over 50 per cent

The question naturally suggests itself what can be done when, owing to intermarriage, an accumulation of one or more severe hereditary diseases has occurred in a group of a population An efficient remedy is as a rule that of getting such a group spread in the population. The hereditary diseases due to latent genes are generally rare, and if spread in a large healthy population they apparently disappear completely In such a large population chance will rarely bring 2 carriers together But, of course, the pathogenetic gene does not disappear, so this procedure still involves a certain risk.

Which stand-point ought one in general to adopt towards consanguineous marriages? Should, for instance, first-cousin marriages be unconditionally advised against? The answer must be: no, in the cases of healthy families Many cousin marriages with healthy offspring are known Otherwise with families in which one or more severe diseases may be latently inherited. In families displaying, for instance, hereditary mental deficiency, schizophrenia, or severe physical deformities we must advise against intermarriage.

Chapter 10

SEX RATIO AND SEX DETERMINATION

Sex Ratio The significance of the sex chromosomes for the determination of sex has previously been mentioned One sex, *which is heterozygous for the* sex chromosomes, in humans the male, produces *in equal* proportions 2 types *of* gametes containing 1 X- *or* 1 Y-chromosomes respectively The homozygous sex, in humans the female, produces only one type of gametes, all containing 1 X-chromosome. It *is therefore* to be expected that at fertilisation XX and XY zygotes are produced *in equal* proportions, i e 50 per cent of each sex

Experience shows in fact that the two sexes are almost equally represented. Minor deviations occur, however, both in higher animals and in man

Among humans the number *of boys born* slightly exceeds that of girls In Copenhagen for instance, there were 158,240 live births during the period 1926-1940 Of these, 51 29 *per cent* were boys and 48 71 per cent girls Out of 4010 stillbirths within the same period 55 24 per cent were boys and 44 76 per *cent girls*

In the stated instance the sex ratio is given as the fraction of males or females in the total number of new-born The sex ratios are, however, often

European princely families reigning in 1918 descended from Louis the Eighth of France, and in this large family about 40 members are supposed to have suffered from schizophrenia.

In such a family the loss of ancestors is conspicuous. Each person has 2 parents and, where marriage of siblings cannot take place, 4 grand-parents But the number of great grandparents, great-great grandparents, etc. will be reduced in proportion to the degree of intermarriage. The chance that the same pathogenetic gene occurs in both conjugal partners is therefore greater in such families.

If no consanguinity occurred, the number of ancestors of any one individual would be 2^n n generations back. As the population of the earth was far smaller in former days than now it is evident that the present population must to a great extent descend from the same ancestors. Consanguinity must be much more extensive than can be elucidated. As a matter of fact we cannot distinguish sharply between genetic unrelatedness and consanguinity.

The latent genes for diseases may have arisen in the remote past and been transmitted through the families for centuries without manifesting themselves, because of their rare existence, until, possibly owing to intermarriage, 2 genes for the same disease meet in one individual who then becomes affected.

Numerous inheritable diseases not infrequently arise by mutation. The possibility therefore exists that, in case of extreme intermarriage through many generations, a phenomenon apparently to be regarded as family degeneration may occur even in healthy families.

Simultaneously with intermarriage a selection often occurs in the negative direction Mental defectives, epileptics, asocial individuals, etc. generally choose conjugal partners among their equals. This may lead to more or less closely attached social groups comprising only a few greatly entangled families. In intermarried families of this kind diseased, defective, or abnormal individuals *may occur in great numbers Both in urban and rural districts we occasionally* find such groups, whose members stick closely together and intermarry, living isolated from the remaining community (*vide* p 294).

Intermarriage does not exclusively lead to development of unfavourable phenotypes. Valuable properties also exist, of course, which relatively often occur in the homozygous form in the case of consanguinity Many instances can be mentioned of outstanding personalities whose parents were cousins, e g Charles Darwin It is difficult to prove that such better-than-average types appear as the result of the homozygosity of valuable recessive genes, but this is not unlikely. It may also be mentioned that the probability of Rh incompatibility between mother and foetus is smaller in consanguineous than in non-consanguineous matings.

SEX DETERMINATION Up to a certain point of time in ontogenetic history the sex develops under the influence of chromosomal and autochthonous substances produced in all body cells and called chromosomal hormones But after that time the incretoric hormones, produced in the endocrine glands, begin to occur These gradually become of increasing importance for the development of the sexual characters

The sex-determining genotypic factors may be attached partly to the sex chromosomes, partly to the autosomes, and partly to the protoplasm of the egg cell This has been observed in various lower organisms, but it is uncertain to how great an extent we may generalize from these observations.

TRIPLOID INTERSEXES In the fruit fly the sex-determining factors are attached to the X-chromosomes and the autosomes, and sex results from a balance between male and female factors. The important thing is the *proportion* of X-chromosomes to sets of autosomes. Under normal conditions the body cells of *Drosophila melanogaster* contain 2 sets of autosomes, while the mature sex-cells contain 1 set. Each set consists of 3 chromosomes (*vide* Fig. 11) Further, there are found, in the male 1 X- and 1 Y-chromosome, and in the female 2 X-chromosomes Each set of autosomes being termed A, normal males get the formula 2A + X + Y and normal females 2A + 2X. A male is characterized as an individual producing male gametes, a female as an individual producing female gametes. All other differences between the sexes are secondary sex characters

During meiosis there sometimes occurs in the female a *non-disjunction* of the 2 X-chromosomes, which then pass to the same gamete. The egg cells then do [illegible] or A
If such e[illegible] + X
or A + [illegible] the following zygotes

2A + 3X superfeminine, die as a rule
2A + Y die
2A + X sterile male
2A + 2X + Y normal female

2A + 2X + Y being a normal female it must be the 2 X-chromosomes which determine the female sex But the Y-chromosomes are not without effect either, for males having the formula 2A + X, with no Y-chromosomes, are always sterile; they produce immobile infertile sperm cells

That it really is the proportion of X-chromosomes to sets of autosomes which determines the sex in the fruit fly has, in addition, been demonstrated

indicated as the number of males per 100 females. The number of boys at birth always exceeds that of girls; but the sex ratios vary from country to country, from about 101 boys to 100 girls up to 113 boys to 100 girls

The proportion of boys to girls at birth is often called the secondary sex ratio, in distinction from the primary sex ratio, i. e. the ratio at the time of fertilisation. Differing views have been advanced with regard to the primary sex ratio. Previously it was believed to be very high, more than 200 males to 100 females. The number of prenatal deaths should be much higher in males than in females. It had been found, from comprehensive observations, that stillborn foetuses and babies showed a greater number of males than females This statistical enumeration is, however, based on reports from medical practitioners and midwives, and it may be a result of misclassifying some of the female stillbirths as male. The external genital organs of the female embryo or foetus with a relatively long clitoris are easily mistaken for male genital organs with a penis by people without specialized training in embryology.

Recent investigations, in the Department of Embryology of the Carnegie Institution, Washington, among others, seem to show that the sex ratio remains fairly unchanged during prenatal life, being approximately the same as a birth, 108 males to 100 females. This bears out the well-known experience that a careful analysis of a limited number of observations often gives a different result from that of statistics based on many superficial observations

In childhood the mortality is higher among boys than among girls, so that among young people the 2 sexes are almost equally represented. As the higher mortality rate for males than females continues, there is a preponderance of females in the older age-classes, as is also the case in the total population.

The sex ratio is not the same in urban and rural districts In towns the women are in the majority and in the country the men

Among some lower animals the sex ratio may differ very considerably from 1 :1, and the distribution of the 2 sexes may be greatly influenced by environmental factors, e g time of fertilisation or the surrounding temperature

Certation implies the competition between pollen tubes or sperms having different genotypes leading to their unequal chances of accomplishing fertilization Perhaps sperms containing a Y-chromosome are favoured as compared with sperms containing an X-chromosome in the race to penetrate the ovum

The term *selective fertilization* have been used for the process of selection by the ovum of biologically advantageous pollen or sperms Mixtures of pollen or sperms from several male individuals have been used in the expectation that the gametes of suitable genetic compositions should fuse Furthermore it has been supposed that ova carrying a gene causing a certain disease should preferable be fertilized by sperms without the gene causing this disease. Nothing to that effect has, however, been proved, there is so far no evidences for these conjectures

Fig 16—Different sexual types of the fruit fly with indications of the chromosome combinations Above to the left normal female (2A + 2X), above to the right intersex (3A + 2X), below to the left "supermale" (3A + 1X), and below to the right "superfemale" (2A + 3X) (After Bridges).

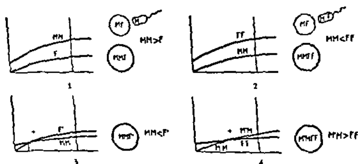


Fig 17—Diagrammatic illustration of the sex determination in man, if human intersexuality is supposed to be of the diploid type 1 Normal male. MM > F throughout life 2 Normal female FF > MM throughout life 3 Male intersex F' is strong The F curve cuts the M curve at the "switch-over" point and remains over it the rest of life 4 Female intersex M' is strong The M curve cuts the F curve and remains over it the rest of life

through extensive cytological investigations and crossing experiments. The following chromosome combinations have thereby been procured in a number of individuals, some of which showed deviating sex characters (Index denotes the proportion of X-chromosomes to sets of autosomes):

	Index
2A + 1X normal male	0 5
2A + 2X normal female	1.0
3A + 3X normal female (triploid)	1 0
2A + 3X superfeminine	1.5
3A + 2X intersex (triploid intersexuality)	0 66
3A + 1X supermasculine	0 33

The X-chromosomes must therefore be supposed to contain genes of which some tend to produce maleness and some femaleness, but with a preponderance of female-producing genes. The autosomes carry genes which are chiefly male-producing. The total female-producing tendency of an X-chromosome is greater than the joint male-producing tendency of a complement of autosomes.

The type 3A + 2X is called a triploid intersex, a mixture of male and female parts. The supermales have all male characters exaggerated, and the superfemales all the female. They are both sterile The haploid individual is unknown among fruit flies, but probably occurs among other species, e g. bees and ants Where haploids occur they are always males

Diploid Intersexes In experiments concerning crossbreeding of various races of the Gipsy moth *Lymantria dispar* from different parts in Europe and Asia interesting observations have been made regarding the quantity or strength of the sex-determining genes. In *Lymantria* the female sex is heterozygous, with a male element, M, in the X-chromosomes and a female, F, in the Y-chromosomes. The autosomes and the cytoplasm likewise contain sex-determining factors, here with female preponderance The egg cells have the formulae FM and F, the sperm cells always M. This can give the 2 zygotes MMF, which are normal males, and MF, which are normal females, if M and F harmonize with each other By crossing different races of which one has a weak M and the other a strong F or *vice versa* we obtain individuals which are intersexual. In this form of intersexuality no chromosomal anomalies have been demonstrated. It has therefore been designated diploid intersexuality

By crossing experiments of this kind we can produce any degree of intersexuality, a fact which shows that it is not a question of incidental anomalies.

in animals These may therefore actually be regarded as rudimentary hermaphrodites No person is completely masculine or completely feminine; life begins with potentialities for either sex.

True hermaphrodism is rare in man But from human pathology we know a great many forms of intersexuality, both physical (genital deformities, gynaecomastia, androtrichosis, etc.) and mental (homosexuality, bisexuality, feminism, virilism, etc), which may be of great importance for the individual and for society The intersexual conditions may be present at birth, or heterologous sexual characters may develop sooner or later in otherwise normal individuals

Earlier classifications of hermaphrodism were mainly descriptive:

A distinction has been made between *true hermaphrodism* and *pseudohermaphrodism* In true hermaphrodism both female and male sexual gland tissue is found in the same individual It may be germinal or glandular according to whether mature germ cells or only immature sexual gland tissue is present.

The ovarian and testicular tissues are generally found in one organ (ovotestis). As might be expected the ovarian portion then forms a covering round the testicular portion. The central testicular tissue may, however, have commenced the descent alone, and ovarian and testicular tissues may then lie completely separated from each other. Ovotestis may occur on one or both sides, or we may find ovarian tissue on one side and testicular tissue on the other True hermaphrodism is, as stated, extremely rare in man Concurrence of mature egg cells and sperm cells in one individual has never been observed The sexual gland tissue of true hermaphrodites is generally almost undifferentiated, and it early presents regressive changes

A much more frequent phenomenon is pseudohermaphrodism, where only one type of sexual gland tissue occurs If this is testicular tissue we speak of *male*, and if ovarian tissue, of *female pseudohermaphrodism* (also called pseudothelia and pseudoarrhenia respectively) If the external genitals are heterosexual the *pseudohermaphrodism* is said to be of the *external* or copulative form If it is the internal genitals that differ, we have the *internal* or tubular form Finally there is the type which may be called *extragenital pseudohermaphrodism*, under which we must include, for instance, certain anomalies of hairiness, gynaecomastia, abnormal bodybuild, and, also at least theoretically, homosexuality

Goldschmidt, on the basis of experience concerning intersexuality in birds and mammals, claimed that only female intersexes occur in man, never male.

In female intersexes the sex should then at some time or other switch over from female to male If the switch occurs during adulthood, only a slight degree of intersexuality will result, corresponding almost to the sequels of castration or mild virilism If the switch occurs in childhood, the intersexuality becomes somewhat stronger Finally, if it occurs *in utero*, it may bring about different forms of intersexuality The most pronounced intersexual condition, though not the most complete change, is seen when the switch

but of a law-directed form of intersexuality, which we must also expect to find in other animal species.

These investigations have shown that there is a gradual transition from the normal female through the different forms of intersexuality to the normal male. The male-producing genes or factors act in one direction and the female-producing in the other. A certain ratio between M and F gives normal males, and another normal females. Disturbances of these ratios cause intersexual forms of different degrees

The theory has been advanced, on the basis of experience with *Lymantria dispar* intersexes as well as observations made on higher animals and humans, that the intersexual individuals genotypically belong to one sex, but change at a certain point of time during ontogeny, because the factors of the other sex then preponderate. The earlier the change takes place the more complete will it be In conformity with this fact, the genitals and other sexual characters developing the last should change the fastest and the most completely. An individual that is laid down as a male and changes in the female direction is designated as a *male intersex*. If laid down as a female, it is a *female intersex*.

INTERSEXUALITY AND HERMAPHRODISM IN MAN. All intersexual forms between the 2 sexes appear also to exist in man The normal sexual development occurs here, too, when the right proportion of factors M and F is present, which are, however, in man purely hypothetical. If F has the right preponderance over M a normal female develops, and if M has the right preponderance over F, a normal male But if the F·M ratio lies between these normal extremes, an intersexual individual results The different forms of hermaphrodism and pseudohermaphrodism in man should then be termed intersexuality Ontogenetic and phylogenetic experiences regarding the sexual evolution in man agree to a certain extent with this view; but the conditions are complicated by the fact that the specific sex hormones begin to exert their influence at a certain point of time in life A distinction has been made between embryonic sex hormones (cf chromosomal hormones p 85) and final sex hormones The embryonic hormones are believed to influence the glands themselves and the development of the derivatives of the Müllerian and Wolffian ducts, whereas the final hormones influence the secondary sex characters and the derivatives of the sinus urogenitalis

Different reactions of the soma to the sex hormones are seen, within one individual, where the various organs differ in hormone sensitivity, also in different individuals within a race, and finally in different races within a species.

The organs of both sexes are laid down in humans in the same way as

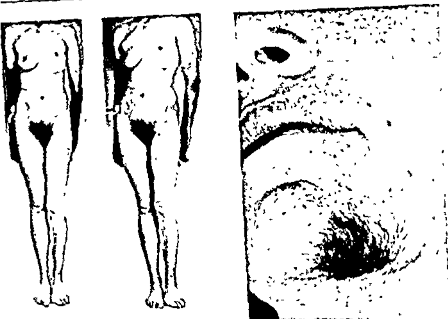


FIG 19.—Gynandromorphism in a patient 22 years old The right body half of female the left of male type, a beard has grown on the left side of the chin 3 photos of the same patient

Gynandromorphism differs from intersexuality. The former is characterized by the occurrence of cells with male as well as with female chromosome combinations in the same individual The intersex is a sex mosaic in time, the gynandromorph an intersex in space

Gynandromorphism may be unilateral, transversal, or mosaic-like.

Unilateral gynaecomastia has been claimed to be explainable as a form of gynandromorphism, but this is open to doubt The genesis of hyperthelia, which is not rare in man, is obscure It is uncertain whether it is hereditary *Gynaecomastia* is not infrequently a familial phenomenon Certain forms of intersexuality in man may probably be regarded as cases of sex mosaic, and several instances of such sex mosaics may be seen in the same family Cases of unilateral gynandromorphism occur in the fruit fly, and in man a similar abnormality may be seen on very rare occasions.

Familial occurrence of intersexuality in its different forms has often been observed It is then generally inherited through females, a fact which can probably be reconciled to the hypothesis advanced above concerning the genesis of intersexuality Pseudohermaphrodism is far more frequent than true herma-

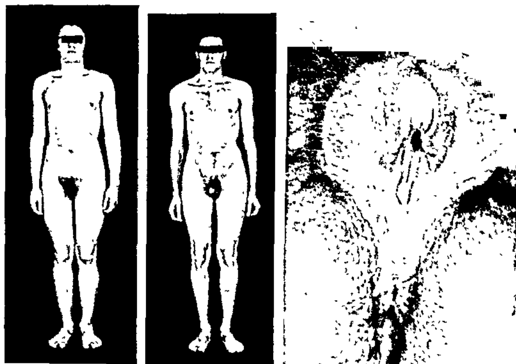


Fig 18 —Male pseudohermafroditism or pseudovaginal hypospadia Intersexuality (possibly female) in two "sisters" 16 and 28 years of age Both are living as females, their gonads are testes They have 8 normal sisters, 1 normal brother and normal parents No other cases of intersexuality known in the family To the right the external genitals of one of the two patients (after Rahbek Sorensen)

occurs at a fairly late embryonic stage, before the Wolffian ducts have been retransformed, but after the Mullerian ducts have reached a certain development An almost normal seminal duct may then be seen side by side with relatively well-developed Müllerian ducts, which may possibly even form a uterus bicornis The sexual glands become ovotestes As a rule no spermiogenesis is seen The sinus urogenitalis has a female appearance If the switch occurs still earlier the change in the male direction becomes more complete The sexual glands become testes, and of the Müllerian ducts only a negligible rest remain, as in the normal male In the most pronounced cases the external genitals also approach the male type in appearance. The intersexuality is then possibly only recognizable by hypospadia, cryptorchism, or similar slight anomalies. The most complete change will result in individuals of a normal male type, but with a female chromosome combination (2 X-chromosomes). Theoretically such persons should only have daughters; but this form of intersexuality has as yet not been observed at all.

is the case with such an anomaly as hypospadia, and on the whole all diseases and defects of the male and the female genitals Sex-limited characters may very well be inherited through the opposite sex. There is a gradual transition from sex-limited to sex-influenced characters The latter occur chiefly in one sex, but may appear in both Many diseases are more or less pronounced sex-influenced. Breast cancer occurs almost exclusively in women; Graves' disease is 10 times more frequent in females than in males, while mental deficiency is more frequent in males than in females. The expression sex limited is, however, often used in the same sense as sex-influenced

Chapter 11

POLYEMBRYONY

One-Egg and Two-Egg Twins. In pure lines comprising descendants obtained from self-fertilisation of a single homozygous parent any variation is due to environmental factors They are therefore particularly fit for the study of the potentialities of variation under different external conditions.

Pure lines do not occur in man, however. The interaction of genotype and environment is here best studied on twins or supertwins.

By *polyovulation* we understand the fact that two or more egg cells are released from the ovaries almost simultaneously within the same copulation cycle, and, if fertilized, give rise to di- or polyzygotic pregnancies. Among many small mammals, e g several domestic animals and the commonly used experimental animals, polyovulation is the rule There are many young in each litter, of which some, however, presumably are monozygotic.

In man and in the larger mammals, where monoovulation is most frequent, polyovulation may also occasionally be seen The results is pregnancies where the individual foetuses differ genotypically, having developed from different egg cells fertilized by different sperm cells But the fertilized egg-cell may also split and thereby give rise to one-egg twins, triplets, etc in the pregnancy concerned This has been definitely ascertained in cattle and man

The only mammal in which the entire process of one-egg twinning is known is the armadillo The nine-banded armadillo living in Texas bears 4 one-egg young at a time It has been possible to follow the embryonic development from the fertilisation, which begins normally, till the first cell divisions have taken place These are followed by a resting period of 3 weeks or more, and when the embryo begins its further development it settles in the uterine membrane, where it forms a trophoblast

phrodism, and the male pseudohermaphrodism (with male sexual glands) is 6 or 7 times more frequent than the female.

It is, however, hardly justifiable to regard all forms of pseudohermaphrodism in humans as female intersexuality. Probably some cases of pseudohermaphrodites genetically are males

All in all we must say that the genesis of pseudohermaphrodism in man is not yet clarified

Hypospadia, which has been explained as a slight form of intersexuality, is no rare abnormality. It is found in about 3 out of every 1000 males and is presumably inherited as a dominant defect with greatly failing manifestation

Homosexuality, no doubt in many cases mentally determined and of a paratypic nature, may occasionally occur as a familial trait, but the mode of transmission has not as yet been definitely elucidated.

Endocrine intersexuality is seen in cases of tumour in adrenal glands or gonads. Most common is virilism in females, due to adrenocortical tumours or adrenocortical hyperplasia. Testicular and ovarian neoplasms can likewise produce the hormones of the opposite sex and thereby condition a sex transformation Androblastoma includes neoplasms originating from potentially testicular cells. In a man with gynaecomastia a feminizing testicular androblastoma has been observed, i.e. a feminizing testicular tumour of the same structure as a virilizing arrhenoblastoma of the ovary.

Feminizing oestrogen-producing Sertoli cell tumours have been observed in the testis. Masculinizing ovarian tumours may be classified as androgen-producing Leydig cell tumours of the ovary.

The study of the lipoidal hormone-producing tumours provides an opportunity of localizing the physiological production of androgen and oestrogen hormones respectively to cells of various types in the normal human testis (Teilum) The lipoid content of germ cells resp Sertoli cells, and interstitial cells determine the hormonal equilibrium in the human male We do not know to how great an extent this balance is hereditary, but it seems natural to analogize it with the genetic balance between male and female factors

SEX-LIMITED AND SEX-INFLUENCED CHARACTERS Sex-limited characters are expressed in one sex only, or at least differently in the 2 sexes But they are inherited like other autosomal traits They differ from the sex-linked, with which they must not be confused, by not being due to genes carried in the sex chromosomes

The primary and secondary sex characters must be reckoned among the sex-limited properties Certain diseases must, of course, be sex-limited Thus

normal mental characters Here we must consider the fact that a pair of one-egg twins, owing to their greater similarity, make for themselves a more similar environment than do two-egg twins, even if the two partners of each pair grow up under apparently identical external conditions. The twin method has therefore proved unsuitable for the study of the dependence of normal mental properties on hereditary factors Numerous psychological twin studies have been made, but the results are not particularly elucidative. They have contributed mainly by throwing a light on the intricacies of the complex of genetic and environmental factors which together determine the development of the normal human psyche

THE FREQUENCY OF TWIN BIRTHS. The frequencies of twin births vary from country to country The white race has a very much higher twin frequency than the Mongol race The twin incidence is higher in the Northern European countries than in Germany, and much higher than in Mediterranean countries

The percentage of twin births to total births varies from 1 8 per cent (Belgium) to 0 30 per cent (Chinese in San Francisco), and even to 0,01 per cent in Cochin China In the U S A 1922-36 1 in about 89 of all white births and 1 in 71 of all Negro births were twin births

In the Scandinavian countries about 1 in 80 births is a twin birth Twins being less viable than other infants we may here reckon that in the entire population 1 out of each 50 is a twin.

Furthermore, in Scandinavia about 25 per cent of the twins born are identical, while 75 per cent are fraternal.

In some other countries the proportion of one-egg to two-egg twins is quite different In Japan, for instance, where twin births constitute only 0.4 to 0 8 per cent of the total number of births, about 72 per cent of all new-born twins are of the one-egg type The frequency of one-egg twins is probably about the same all over the world, while that of two-egg twins varies from one country to the other

One-egg twins are always same-sexed, while among two-egg twins same-sexed and opposite-sexed pairs are nearly equal in number By doubling the number of opposite-sexed twin pairs in a certain series we thus obtain the number of two-egg twin pairs By subtracting this number from the total number of twin pairs in the material we find the number of one-egg pairs

MULTIPLE BIRTHS It has been observed that in some countries there is one twin birth to 80 single births and it appears that there is one triplet birth to about $80^2 = 6400$ single births, and one quadruplet birth to about every $80^3 = 512000$ single births, and so on Greulich actually found that out of more than 120 million births collected from registration bureaus in 20 countries

After the formation of the embryonic shield the embryo splits into 2 symmetrical halves, which again split in a plane at right angles to the former. This gives 4 embryonic cell groups from which 4 foetuses develop The young are similar in all respects and always of the same sex Cell groups constituting only part of the total *anlage* may thus at *very early developmental stages* be *totipotent*, so that new individuals may develop from them. The period for this process is, however, short. Fairly young embryos already contain differentiators. The developmental trend of the cells is determined long before the individual organs are distinguishable

Polyembryony, the tendency to splitting, is present in all living tissue. The formation of one-egg twins has been explained as a kind of alternation of generation, corresponding to what is known from lower animals, where sexed generations interchange with unsexed.

In man up to 6 foetuses, or perhaps even more, have been observed in one pregnancy, but no member of these sextuplets has survived longer than a few hours. *The greatest interest is, however, associated with twin pregnancies,* which are by far the most frequent

Two-egg or *biovular* or *dizygotic* or *fraternal twins* occur when 2 separate egg cells are released almost simultaneously from the ovary and become fertilized each by a different sperm cell. The 2 foetuses develop simultaneously in the uterus, but do not resemble each other more than siblings generally, and they may, like these, be of one or different sexes

One-egg or *monovular* or *monozygotic* or *identical twins*, on the other hand, develop from one fertilized egg cell, one zygote, which has split into two after the fertilisation to form 2 independent foetuses One-egg twins, derived from one fertilized egg cell, possess the same hereditary factors They are therefore always same-sexed and on the whole similar as regards all hereditary characters.

If we want to ascertain whether a character, e g a disease or an abnormality, depends on hereditary factors, we can roughly do so by investigating whether it behaves alike *(is concordant)* or differently *(is discordant)* in 2 one-egg twins. If the disease is definitely hereditary and has a high frequency of manifestation, it always manifests itself alike in both twins If the development of the disease depends to a somewhat greater extent on environmental factors, we may in some cases find discordance, and if not hereditary at all, the disease is just as often discordant in one-egg twins as in same-sexed two-egg twins

This argument presupposes that pairs of one-egg and two-egg twins grow up under approximately the same external conditions This is justifiable if we use twin methods for investigations of the significance of hereditary factors for easily recognizable traits, such as severe physical or mental diseases and defects

This, however, is not the case with less pronounced peculiarities, e g

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FIG 20.—Triplet sisters, 2 of them of one-egg origin, to the left at a young age, to the right older If in each picture we look at the two sisters to the left they constitute a two-egg twin pair, while the two to the right constitute a one-egg pair (After Oluf Thomsen)

one twin birth corresponded to 85 2 single births, one triplet birth to $(87.3)^2$, and one quadruplet birth to $(87.5)^3$ single births.

Triplets may be of one-egg origin, or have developed from 3 different eggs, or 2 of them may be identical while the third has developed from an independent egg (*vide* Fig 20). One-egg triplets are the result of incomplete double one-egg twinning The single egg divides once to form twin embryos, and then one of these twins divides again. If the other twin also divides the result will be one-egg quadruplets Quadruplets and quintuplets likewise occur either as identical or in different combinations, originating from two or more eggs.

THE CAUSES OF TWINNING. Such facts as race, climate, and the mother's age are of importance for the occurrence of polyembryony In animals which normally present polyovulation the litters differ greatly in size in the different races within the same species. We may therefore conclude that the tendency to polyovulation is a hereditary trait In man there is probably also an inherited tendency to polyovulation, but its penetrance is low. The tendency to produce two-egg twins must, of course, be related particularly to the mother, and may presumably be both idiotypic and paratypic. It seems, however, as if the genetic constitution of the father can also contribute to the production of two-egg twins Twin births often occur as a familial phenomenon Siblings of parents who have got twins seem more likely to get twins than others A woman who has once born two-egg twins has a greater chance of doing so again than women who have not born twins.

Two-egg twins become more frequent with increasing ages of the mothers

until the age of 37, after which they are rarer. One-egg twins are equally frequent at any age of the mother. The incidence of two-egg twins is higher in rural districts than in cities. The theory has been advanced, on the basis of experiments with fish embryos, that the primary cause of one-egg twinning is a temporary stoppage of development at a critical stage.

THE EMBRYOLOGY OF TWINNING. Previously it was universally believed that the question of mono- or dizygosity could be settled from the condition of the afterbirth. Two-egg twins were thought always to be dichorionic and biamniotic, while the one-egg pairs should have a common chorion. The septum between the 2 amniotic cavities should thus consist of only 2 amniotic membranes. In the cases of two-egg twins, on the other hand, it should always consist of 4 layers, 2 amniotic and 2 chorionic, or chorionic tissue should at least always be demonstrable on microscopical examination between the 2 amniotic layers.

The views concerning this fact have changed considerably within recent years, after the foetal membranes of a great number of new-born twins have been closely examined and the results compared with those of the so-called polysymptomatic similarity test (*vide* p. 145). The similarity method has gradually attained such a degree of perfection that by this alone we can nearly always determine whether mono- or dizygosity is present. It may be difficult to classify twin infants, but classification of twins of school age or older is generally easy. In a few cases two-egg pairs born to parents who resemble each other may be relatively alike, and one-egg twins may for some reason or other have grown to differ somewhat.

The examinations showed that about one-third to one-half of one-egg twins are dichorionic. By examining the foetal membranes of new-born twins only about 15 per cent were found to be monochorionic, while about 25 per cent of all twins are identical. This may be explained by the fact that the twin formation, the splitting into two of the fertilized egg or the young embryo may take place at different stages of embryonic life.

The following possibilities exist:

1) *Dichorionic, biamniotic,* one-egg twins are produced if the splitting into two occurs at the early segmentation stage before the trophoblast formation, i.e. before 8 to 12 days of fertilisation, while the egg still lies in the Fallopian tube or has just entered the uterus (in the monkey the embryo lies in the middle of the tube at the 4-cell stage, and in man nidation occurs at the morula stage).

2) *Monochorionic, biamniotic* twins are produced if the splitting occurs after trophoblast formation and nidation, but before the formation of the embryonic shield and area, in other words, before the amniotic cavity is laid down, or presumably between the 12th and the 16th or 18th day. In this connection attention may be called to the

fact that from about a fortnight after conception an increased excretion of chorionic hormone is demonstrable in the urine of pregnant women, indicating that the trophoblast by this time has obtained connection with the mother's circulation

3) *Monochorionic, monoamniotic* twins are produced if the splitting does not occur till the embryonic area has developed and the amniotic cavity been laid down, but before the development of the primitive streak and commencement of a proper organogenesis. This means presumably between the 16th to 18th and the 19th to 21st day after the fertilisation This possibility is rarely carried into effect.

4) *Double monsters (incomplete twinning) are seen if the splitting occurs after the* development of the primitive streak, presumably after the 20th to 21st day of fertilisation. The phenomenon of conjoined twins is supposed also to have other causes, such as recoalescence of 2 completely separated foetuses.

Superfertilisation and Superfoetation. A woman can give rise to a multiple birth from more than one father. In rare cases two-egg twins have different fathers. If 2 egg cells are released not quite simultaneously from the ovary, and the woman at short intervals has sexual intercourse with 2 different men, the result may be two-egg twins with 2 different fathers. This phenomenon, called superfertilisation, has been demonstrated several times, particularly since the introduction of blood group examinations Superfoetation may also occur in humans, if 2 eggs, released at different menstrual periods, are fertilized at different points of time. Twins of different ages then develop in the same uterus. It has been observed at operation and on post-mortem examination But we do not know for certain whether superfoetation can result in viable twins.

Differences of One-Egg Twins One-egg twins always differ somewhat even if they are genetically alike, just as there is a difference between the right and the left side of an individual. Various organs normally present bilateral asymmetry with regard to the median plane of the body; but even symmetrical organs may often display considerable asymmetry We cannot either exclude the possibility of a somatic mutation in one twin of a one-egg pair, resulting in a certain dissimilarity of the twin sibs

Rather considerable differences in one-egg twins may also be due to different blood supplies to the two foetuses, often caused by anastomoses, which place one twin in a more favourable position with regard to blood supply than the other One twin therefore often shows less vigour than the other, or is sterile; in addition such gross defects as for example acardia may be found in one foetus. During the mid-pregnancy period there is a greater difference in weight between one-egg twins than between two-egg, and the same is the case at birth. But after birth the difference is reduced in one-egg

twins, whereas it as a rule increases in two-egg twins The prenatal mortality is higher in one-egg than in two-egg twins

Deformities are more frequent in one-egg than in two-egg twins, probably due to arrested development One-egg twins are on the whole less strongly developed and are very often prematurely born At a very early developmental stage the left side of the embryo is slightly superior to the right in rate of development Right-handedness is merely an expression of a slight superiority of the motor centres of the left half of the brain. The twin developing from the left side of the embryo is generally slightly superior to the other, larger and with greater vigour. This difference may persist throughout life, both physically and mentally

Mirror Imaging in Twins Differences that are not environmentally determined may develop in one-egg twins The twins are *not* always completely alike, *not* congruent In certain respects they may form mirror images of each other Characters which in one twin occur on the right half of the body are in the other found on the left half, and *vice versa*. Such twins are, if placed face to face, symmetrical with regard to a plane straight between them Occurrence of mirror image twins can, of course, be ascertained only if each of a pair of twins displays asymmetry between the two body halves Such twins are called *reversed asymmetrical twins*.

Asymmetry has been demonstrated in the cutaneous pattern of the fingers, the palmar creases, the hair whorls of the crown of the head, dental conditions, the two halves of the face, left-handedness or right-handedness, and many other properties Partial asymmetry has been shown in the position of the viscera, among others, specially the circulatory system, e g. with regard to the site of the aorta. Complete situs inversus viscerum has been observed in but few one-egg twins, whereas this abnormality has been seen in several cases of conjoined twins

Marked reversed asymmetry is demonstrable in one or more organs of about 40 to 45 per cent of all one-egg twins. Such occurs also in two-egg twins, but much more rarely The incidence of left-handedness is twice as high among two-egg twins as in the general population This is conceived to be explainable in the way that a number of the two-egg twins originally belonged to sets of triplets or quadruplets, of which one or more partners were absorbed in embryonic life, or disappeared completely or were present as a papyraceous foetus One of the 2 remaining foetuses would then in some cases originate from the same zygote as one of the absorbed foetuses and therefore relatively often be left-handed This is, however, a hypothesis only, of which we have no proof

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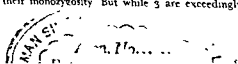


FIG 22 — Above Harelip concordant and reversed asymmetrical (mirror-imaging) in identical twins (from Birkenfeld) Below Harelip and cleft palate in identical twins, concordant and on left side in both (congruent) (from Fogh-Andersen)

demonstrated between twins in a pair with reversed asymmetry than in other pairs No difference has been ascertained with regard to weight, height, length and breadth of the head intelligence quotient, and motor tests, for instance. But there may very well be greater differences in such organs as brain and heart between reversely asymmetrical twins than other one-egg twins.

Mirror imaging presumably occurs when twins arise by splitting of a relatively highly differentiated embryo, in other words, relatively late in the ontogenesis, after the development of the right and left organs has commenced This has been evidenced by a special observation

In May 1934 the so-called *Dionne quintuplets* were born in Canada They were remarkable by being all viable These quintuplets are one-egg, all girls, and their physical as well as mental development, closely followed by specialist experts, show great uniformity The similarity method proved their monozygosity But while 3 are exceedingly



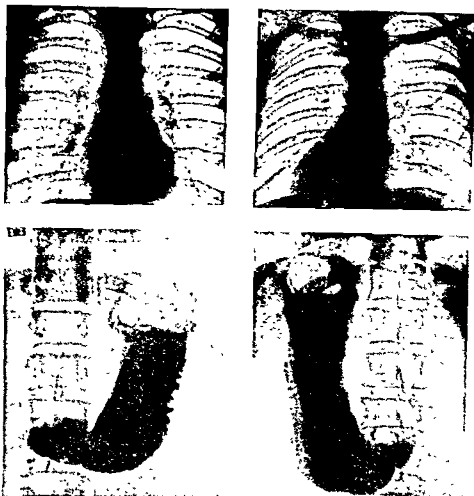


FIG 21 —Discordant situs inversus viscerum in two healthy, monovular twin brothers, 26 years old To the left heart and lung (above) and stomach (below) in the normal twin, to the right in the mirror-imaged twin (After Helweg-Larsen)

The following incidence figures have been stated for the most frequent reversed asymmetries in one-egg twins.

In about 25 per cent one is left-handed and the other right-handed In about 32 per cent the occipital whorls twist in opposite directions in the twin sibs, normally in the clockwise direction, and counter-clockwise when reversed. About 10 per cent present reversed asymmetry with regard to both handedness and hair whorl In about 12 per cent there is found reversed asymmetry with regard to handedness and dental condition and in about 16 per cent with regard to hair whorl and dental conditions

It has been closely investigated whether greater differences could be

Chapter 12

MIXTURE OF SPECIES AND RACES

Crossing may generally take place without difficulty between different races or varieties within the same species. Individuals belonging to the same species have homologous chromosomes, containing in the main the same genes. A normal chromosome conjugation is therefore possible when 2 gametes from 2 different races unite. The harmony may, however, to a certain extent be lost by such crossing owing to a difference in gene quantity, as appears from the previously mentioned (p. 86) crossing experiments with geographically different varieties of the moth *Lymantria*.

Mixture of Species. Different species cannot, as a rule, be mixed. In most cases their chromosome combinations differ so much that fertilisation with normal conjugation is impossible. Occasionally, however, mixture of closely related species occurs in nature, and such crossbreeding can also be carried out experimentally. Hybrids of different species are often sterile, though instances are known of fertile hybrids of this kind. The sterility is probably due to a failing harmony between the chromosomes of the 2 gametes from which the zygote is produced.

In plants a chromosome duplication may occur by crossing of species, so that the hybrid gets a chromosome number corresponding to the sum of the diploid numbers for both original species. The hybrid then does not become sterile and remains constant by continued reproduction. Many new species have no doubt arisen in this way, a fact which has been of importance in evolution. Many cultivated plants are likewise a result of such crossbreeding.

As mentioned in the chapter on inbreeding, crossing of 2 inbred lines often leads to the occurrence of new particularly strong individuals. This stimulating effect of hybridity is called *heterosis*, or hybrid vigour. It is due to the fact that the crossing involves heterozygosity for several genes. Similarly crossing of different species or varieties often gives hybrids that are particularly vigorous and possess valuable properties. Our cereals are most likely the result of accidental hybridisation of wild grasses. Valuable botanical hybrids, e.g. certain rose varieties, can be reproduced vegetatively by slips. The phenomenon of heterosis is utilized in the breeding of domestic animals, where different inbred, improved, and therefore delicate races are crossed. This gives good and strong working animals, which, however, are not suitable as breeders. The improved races are therefore used for continued breeding.

alike, 2, Marie and Emilie, differ slightly from the others. They weigh less, are smaller, and on the whole developmentally deficient both physically and mentally. In this connection there is reason to note that the 3 bigger ones show no mirror imaging, whereas the 2 smaller ones are reversely asymmetrical in some respects, one being left-handed and the other having the hair whorl twisted in the opposite direction of the 4 others.

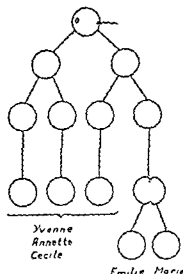


FIG 23.—Diagrammatic illustration of the genesis of the Dionne-quintuplets A fertilized egg has divided into 2, each of which has again divided into 2 One of the resulting 4 eggs has divided once more This having occurred relatively late, the twins produced, Emilie and Marie, are mirror-imaged to a certain extent

As indicated in Fig 23, Emilie and Marie must be supposed to have developed by splitting at a later stage of the ontogenesis than the others. These two therefore present mirror imaging, a fact which seems to bear out the theory that reversed assymmetry occurs when the splitting takes place relatively late in embryonic life

Another theory of mirror imaging is based upon experimental studies of reversed fish embryos showing that reversed asymmetry can be a product of arrested development This fits in well with the observation that in man individuals with reversed internal structures, situs inversus viscerum, are frequently subnormal in other ways

from a less civilized race This has led to the mistaken conclusion, based on experience with such hybrids, that race mixture in itself is unfortunate.

Race pathology is particularly concerned with non-hereditary diseases But various observations have been made which prove the existence of a relationship between hereditary disease and race. Certain diseases are unknown in some races; or the frequency of a disease varies from race to race. Erythroblastosis foetalis, for instance, shows a different frequency in different races. Sicklaemia seems to be restricted to Negroes, and Cooleys anaemia or thalassaemia (v p 246) to people of Mediterranean racial descent Pernicious anaemia is relatively common in North-Western Europe, more rare in South Europe and almost never seen in Asia and Africa Infantile amaurotic idiocy is said to be frequent among Jews, and so on It is, however, as yet too early to draw general conclusions regarding differences in racial frequencies of pathogenetic genes

When two or more races live together in the same territory the miscegenation sometimes proceeds at a slow pace and at other times more rapidly, resulting in amalgamation or assimilation A mixed race may show an increase of variability in some characters and a decrease in others

There is no reason to regard the pure race as archetypical or particularly valuable That which is generally designated as a pure race is a result of a long period of development in isolation, which has rendered possible a *selection* of certain properties, which remain constant as long as race mixture does not take place It is therefore hardly possible to lay down general rules as to whether crossing of races is advantageous or the reverse If the races that have existed through several centuries can be supposed to have improved by selection, and therefore have a particularly harmonious and well-balanced constitution, race mixture can in certain cases be expected to lead to production of less harmonious and well-balanced types On the other hand, race mixture may probably also cause production of successful combinations, which may give rise to quite new race types Which type of human race is the most valuable is after all a matter of opinion The assumption of a superiority of certain races over others lacks any *scientific basis* He who prefers a population where all think and feel alike must be opposed to mixing of the races If, on the other hand, one regards the society as the most fortunate which shows greater variation, contains many different human types, many *kinds* of genius, and which gives scope to development of human intellect in its rich, though perhaps also sometimes dangerous variety, there is no reason to fear race mixture

The possibility has been suggested that the rather considerable increase in body height seen in various civilized countries within the past hundred years or so (*vide* p 144) might in part be due to the fact that, owing to the break-down of isolates, the populations of these countries have been mixing to a greater extent than previously. However, improved nutrition and a more healthy mode of life have no doubt likewise contributed a great deal

The hybrid produced by mixture of species as a rule resembles both parents almost equally, both in appearance and other properties. But it does not always seem to be a matter of indifference whether the father or the mother originates from one or the other of the 2 species that are mixed. This is very likely true, partly because a cytoplasmic effect may be conceived to be transmitted with the egg cell, and partly because other genes than the sex-determining ones may be carried in the X- and Y-chromosomes The mule, produced by crossing a male donkey with a mare, differs from the kinny, which is the offspring of a female donkey and a stallion.

Mixture of species with greatly differing chromosome numbers, as is possible in the case of plants, is generally most successful when the maternal organism has the highest chromosome number. Thus, it is easier to produce a wheat-rye hybrid when wheat (haploid chromosome number 21) is used as the maternal and rye (chromosome number 7) as the paternal organism than the reverse.

Many hybrids of different species are known among both birds and mammals. The horse may be crossed not only with the donkey, but also with the zebra, the dromedary may be crossed with the camel, the lion with the tiger, etc The hybrids, specially the male, are often sterile

We know no instances of crossing of humans with individuals belonging to other species Crossing with anthropoid apes *a priori* seems within the limits of practicability, especially now that we command methods of artificial insemination But this has never been stated to have taken place. The accounts frequently passed from mouth to mouth that bestiality with lower animals, e g. dogs, has led to offspring are fictitious

RACE MIXTURE The various human races can mix freely, and their offspring do not become sterile No reports are available proving that crossing of human races should give biologically inferior offspring But such a crossing may naturally cause difficulties owing to prejudice, or if the 2 races crossed belong to very different cultural levels In the latter cases the hybrid may feel that he belongs nowhere, neither to one nor to the other of the parents' races Race mixture may also give rise to unfortunate selection, because it is often asocial and criminal persons from the higher race who mate with persons

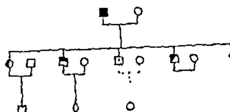


FIG 24.—Instance of pedigree See text

census registers, archives, Probate Court records, generic descriptions, hospital records, death certificates, etc.

The pedigree is often drawn diagrammatically (*vide* Fig 24). Previously the symbols ♂ and ♀ were often used in such pedigrees for males and females respectively, but now the symbols □ and ○ are more commonly employed, together with the following other symbols:

□	Normal male
☒	" " , dead in childhood, under 7 years
○	Normal female
⊘	" " , dead in childhood, under 7 years
△	Normal person, sex unknown
⚠	" " " " , dead in childhood
◊ 4	Normal siblings, the figure below gives the number of siblings
•	Abortion or still-birth
□ ○ ○ □	Normal siblings (= sibs = brothers and sisters)
○ □⧖□	" " including identical twins
○ □⧖○	" " " non-identical twins
□ ○ joined below	Marriage
□ ○ □ joined below	Married twice
□ ○ joined by dotted line	Illegitimate union
■ ● ◨ ◓	Abnormal males and females.

It is rarely possible to draw pedigrees comprising more than about 10 generations. Often only the data of a few generations can be procured, and occasionally the family is quite unknown Hereditary diseases which give characteristic, easily recognizable signs and symptoms may sometimes be traced 300 to 400 years back, in some cases even still longer

The following instances may be mentioned of hereditary diseases and abnormalities traceable through many generations Dominant *night blindness* occurred in a large Danish family, where the anomaly could be traced 9 generations back to a man who, according to tradition, acquired it while leading a miserable life during a war in 1675

Part II

MEDICAL GENETICS

CHAPTER 13

GENETIC STUDIES ON MAN

Medical genetics is concerned with the study of hereditary factors in man, their origins, their frequencies, the rules according to which they are inherited, and the ways in which they manifest themselves in the individual.

Genetic studies on man are beset with difficulties which are less conspicuous in cases of plants and animals. Crossing experiments are out of the question. The numbers of offspring are often small, and each change of generation lasts several decades.

On the other hand, the human populations are so large and thoroughly investigated with regard to both normal and pathological traits that we can find almost any crossing imaginable in them, and thus collect sufficient material to study the modes of transmission of most diseases and other properties.

Medical genetics avails itself of the results of ordinary genetics, but in addition it must to a great extent employ its own methods

Family investigations constitute the basis of human genetics Such investigations often start from a single person, called the propositus Pedigrees can then be drawn for the ascendants and/or the descendants of this person

The ascendency pedigree comprises parents, grandparents, great grandparents, etc. It therefore always consists of a certain number of individuals in each generation. 2 in the first 2^2 in the second, 2^3 in the third, etc, unless intermarriage causes loss of ancestors. It may, of course, be extended to comprise siblings of parents and grandparents, etc, and thereby in many cases assume considerable dimensions. The descendency pedigree consists of children, grandchildren, etc of the propositus In some cases it may be of interest to include the siblings of the propositus and their descendants.

Proper pedigree charts are often elaborated, which include ascendants and descendants as well as siblings of the propositus himself, of his parents, grandparents, etc. and their descendants. This is a genealogical task, where, in addition to questioning living relatives, it is necessary to study church registers,

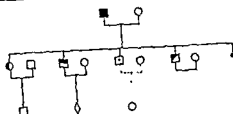


Fig 24.—Instance of pedigree See text

census registers, archives, Probate Court records, generic descriptions, hospital records, death certificates, etc

The pedigree is often drawn diagrammatically (*vide* Fig 24). Previously the symbols ♂ and ♀ were often used in such pedigrees for males and females respectively, but now the symbols □ and ○ are more commonly employed, together with the following other symbols:

- □ Normal male
- ⊠ " " , dead in childhood, under 7 years
- ○ Normal female
- ⊘ " " , dead in childhood, under 7 years
- △ Normal person, sex unknown
- △ " " " " , dead in childhood
- ◇ Normal siblings, the figure below gives the number of siblings.
- • Abortion or still-birth
- Normal siblings (= sibs = brothers and sisters)
- " " including identical twins
- " " " non-identical twins
- Marriage
- Married twice
- Illegitimate union
- ■ ● ◧ ◒ Abnormal males and females

It is rarely possible to draw pedigrees comprising more than about 10 generations Often only the data of a few generations can be procured, and occasionally the family is quite unknown Hereditary diseases which give characteristic, easily recognizable signs and symptoms may sometimes be traced 300 to 400 years back, in some cases even still longer

The following instances may be mentioned of hereditary diseases and abnormalities traceable through many generations Dominant *night blindness* occurred in a large Danish family, where the anomaly could be traced 9 generations back to a man who, according to tradition, acquired it while leading a miserable life during a war in 1675

—79. Hemeralopia has also been described in a large French family, called Nougaret, comprising 2116 individuals, all descendants of a man born 1617 at *Mont Pellier*. In the course of 9 generations he had 134 known affected individuals among his descendants. A third family with hemeralopia has been found in Berner Jura in Switzerland Another instance is *phalangeal synostosis*. The 1st Earl of Shrewsbury, born 1390, was found, during repairs of his burial place, to have had this deformity, which is dominant. It is present in the living descendants of the Earl, after having been inherited through 14 generations The *Habsburg lip* is believed to be traceable through 15 generations by means of written sources, family portraits, and the like, down to Ex-King Alfons the 13th of Spain and his son Jaime A mental disease, presumably *schizophrenia*, has in a princely family been followed through 11 generations from Wilhelm the Younger of Brunswick-Luneburg, born 1535, to King Ludwig the 2nd af Bavaria, who in 1866 committed suicide by drowning in Starnberger See together with his physician in attendance *Huntington's chorea* has in several cases been traceable through 10 generations Various other similar instances might be mentioned

However, in the cases of most diseases, the diagnosis cannot be made on the basis of descriptions by laymen; and even if case records from physician or hospital are available from earlier times, these cannot always be relied upon, because the diagnostic criteria may have changed in the course of time.

As a rule therefore hereditary diseases can be traced only few generations back in the family In general this is also sufficient. A hereditary taint in a remote ancestor is of relatively little importance owing to the great number of ascendants

Family investigations often reveal a greater or smaller *hereditary taint* A person is designated as tainted if hereditary, or supposedly hereditary diseases occur in relatives

The hereditary taint may be difficult to assess If not seen in the nearest relatives it may be of little or no significance One is often in doubt whether the diseases regarded as hereditary really are so Furthermore, we do not know exactly whether a predisposition to one disease may play a part on the occurrence of another It is, for instance, difficult to say to which extent tainting with alcoholism may be regarded as predisposing to psychopathy, schizoidy to schizophrenia, etc.

In case of *heterogeneous predisposition,* e.g to schizophrenia and manic-depressive psychosis, the genes for the individual diseases are naturally inherited independently of each other, unless they are linked We cannot, however, exclude the possibility of a certain interaction of the signs and symptoms of the different hereditary diseases, when the genes for them are present in the same person

The assessment of a hereditary taint is actually almost identical with the task of making a genetic prognosis The possibilities of doing this are described later. First it might be as well to mention the rules used in calculating the probability and frequency of a hereditary disease in the population as a whole

Chapter 14

PROBABILITY

Probability and Frequency The probability calculation is concerned with forecasts regarding certain occurrences of which the outcome must be thought to be "a matter of chance", which means that we do not have a sufficiently exact knowledge of all the circumstances on which the outcome depends to say for certain what is likely in the individual cases. In this sense it is "a matter of chance" whether an expectant mother will have a boy or a girl, or whether a germ cell from a heterozygote Aa will contain the gene A or the gene a.

Under certain conditions the probability can be calculated *a priori*. This is, however, only the case if the various events in question are "equally possible", i.e. if one or more of the events are not favoured by some outside effect or other. The probability is then defined as the fraction formed by the "favourable" event divided by all possible events

$$p = \frac{f}{n}, \text{ where } 0 \leqq p \leqq 1$$

Such an "equal possibility" is present in throwing of dice, for instance, or we may hypothetically suppose it to be present and make calculations accordingly, as is often done in genetics. By way of example we may say that the probability that a germ cell from a heterozygote Aa contains the gene A will be 50 per cent.

In biological statistics, however, "equally possible" events do not generally occur. The probability must here be calculated empirically, *a posteriori*, on the basis of the incidence of the phenomenon concerned.

If in one or more series of n observations we find n_x with a certain event, e.g. n_x male individuals or n_x with a certain disease, we call n_x the absolute frequency of the event a and define the probability p as follows:

$$p = \lim_{n \to \infty} \frac{n_x}{n}, \; 0 \leqq p \leqq 1$$

The limits of probability are 0 and 1.

In practical calculations it is, of course, impossible to allow the material to be investigated to grow indefinitely. We can only determine $\frac{n_x}{n}$ for the largest n possible, and the value found is then often designated as the probability. Strictly, only the probability sought for can be estimated in this way, but the extreme limits of the actual probability can be indicated.

Mating of Aa ~ Aa theoretically gives an equal possibility of 4 offspring combinations (AA, Aa, aA, aa), and the probability of, say, aa is then 25 per cent. The same result would be achieved empirically by examining a great number of children of the stated parent combination, if no particular influence interfered with the "equal possibility".

As we cannot investigate infinitely large materials, but must confine ourselves to samples from the population made the object of study, we must take great care that the sample taken is representative, i.e. of such a quality as to give a true picture of the population

RULES FOR CALCULATION OF PROBABILITIES. I. The probability that one or another of two (or more) events will occur is the sum of the separate probabilities

Let p_a indicate the probability of occurrence of an event a, and p_b of an event b. If the two events cannot occur simultaneously the probability p_{a+b} that either a or b occurs is

$$p_{a+b} = p_a + p_b$$

If p_a is the probability of getting blue eyes and p_b that of getting brown eyes, the probability of getting either blue or brown eyes is $p_a + p_b$ The probability of not getting blue eyes is $1 - p_b$

If two events, a and b, do not preclude each other (e g blue eyes and hypermetropia) both will in some cases occur simultaneously Is the probability that both events occur p_{ab}, then the probability that either a or b occurs is

$$p_{a+b} = p_a + p_b - p_{ab}.$$

II. The probability of two (or more) independent events coinciding is the product of the two (or more) separate probabilities

If the events a and b are mutually independent, i e if the probability of one event is independent of whether the other has occurred or not, the probability p_{ab} that both a and b occur is the product of the probability p_a that a occurs and the probability p_b that b occurs,

$$p_{ab} = p_a \times p_b$$

If the probability of meeting the gene A in a population is p and that of meeting the allelomorph a is q, then the probability of formation of the zygote AA is p^2, and of aa q^2. The probability of the zygote aA is pq, and of Aa likewise pq. As, however, Aa is equal to aA the probability of the occurrence of this type of zygote is 2 pq. The same result might be achieved by the

following argument: Only 3 genotypes are possible: AA, Aa, and aa. Aa must therefore occur at a frequency of $1 - (p^2 + q^2) = 2pq$, as $p + q = 1$.

It is often expedient first to find the probability of the "opposite" event to that asked about, as appears in the following instance

On the assumption of recessivity for a disease the probability of affected offspring of the parents Aa ~ Aa is 25 per cent. What is the probability of at least one affected child in n-children matings? First the probability is calculated that a married couple have n children of whom none are affected: $(3/4)^n$. The probability in question can then be deduced this formula: $1 - (3/4)^n$

The genetic structure of a population remains constant from generation to generation in case of random mating. In the first generation the probabilities of the zygotes AA, Aa and aa are, as stated:

$$p^2, 2pq, \text{ and } q^2.$$

We then have the following probabilities of the different matings:

	AA	Aa	aa
AA	p^4	$2p^3q$	p^2q^2
Aa	$2p^3q$	$4p^2q^2$	$2pq^3$
aa	p^2q^2	$2pq^3$	q^4

By way of example the probability of the mating AA ~ AA is $p^2 \times p^2 = p^4$, and that of AA ~ Aa is $2p^3q + 2p^3q = 4p^3q$ (the probability of AA ~ Aa plus that of Aa ~ AA). Below is shown the probabilities of the zygotes that may arise by the different matings:

	AA	Aa	aa
AA ~ AA	1	—	—
AA ~ Aa	½	½	—
AA ~ aa	—	1	—
Aa ~ Aa	¼	½	¼
Aa ~ aa	—	½	½
aa ~ aa	—	—	1

This gives the following total probabilities of occurrence of the zygotes, as $(p + q)^2 = 1$

AA $p^4 + \frac{1}{2}\,4p^3q + \frac{1}{4}\,4p^2q^2 = p^2$

Aa $\frac{1}{2}\,4p^3q + 2p^2q^2 + \frac{1}{2}\,4p^2q^2 + \frac{1}{2}\,4pq^3 = 2pq$

aa $\frac{1}{4}\,4p^2q^2 + \frac{1}{2}\,4pq^3 + q^4 = q^2$

Mating of Aa ~ Aa theoretically gives an equal possibility of 4 offspring combinations (AA, Aa, aA, aa), and the probability of, say, aa is then 25 per cent. The same result would be achieved empirically by examining a great number of children of the stated parent combination, *if no particular influence interfered* with the "equal possibility".

As we cannot investigate infinitely large materials, but must confine ourselves to samples from the population made the object of study, we must take great care that the sample taken is *representative, i.e. of such a quality* as to give a true picture of the population.

Rules for Calculation of Probabilities. I The probability that one or *another of two (or more) events will occur is the sum of the separate probabilities.*

Let p_a indicate the probability of occurrence of an event a, and p_b of an event b. If the two events cannot occur simultaneously the probability p_{a+b} *that either a or b occurs is*

$$p_{a+b} = p_a + p_b$$

If p_a is the probability of getting blue eyes and p_b that of getting brown eyes, the probability of getting either blue or brown eyes is $p_a + p_b$. The probability of not getting blue eyes is $1 - p_b$

If two events, a and b, do not preclude each other (e.g blue eyes and hypermetropia) both will in some cases occur simultaneously. Is the probability that both events occur p_{ab}, then the probability that either a or b occurs is

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If the events a and b are mutually independent, i.e if the probability of one event is independent of whether the other has occurred or not, the probability p_{ab} that both a and b occur is the product of the probability p_a that a occurs and the probability p_b that b occurs,

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If the probability of meeting the gene A in a population is p and that of meeting the allelomorph a is q, then the probability of formation of the zygote AA is p^2, and of aa q^2. The probability of the zygote aA is pq, and of Aa likewise pq. As, however, Aa is equal to aA the probability of the occurrence of this type of zygote is 2 pq The same result might be achieved by the

taken for granted to occur at random in the population, and individuals of different heredity to have the same chance of procreation This is called panmixia or amphimixia.

But these suppositions, of course, never hold good in their full extent. The human populations are never well-defined, and their composition alters continuously in an incalculable way by migrations and changing conditions of living Panmixia possibly exists with regard to certain normal hereditary characters, e g some blood groups, i.e. they are mixed absolutely equally in the population, because random mating takes place of bearers of these characters, whose average fertility and longevity are the same as in the population Whether or not such neutral alleles exist is, however, unknown.

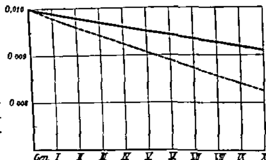


FIG 25—Recessive character Initial frequency 0 01 per cent, equilibrium between negative selection 50 per cent and mutation rate 0 00005 Effect of total elimination of the recessive homozygotes with unchanged mutation rate (————) and effect of total elimination without mutations (-------) through 10 successive generations (after v Hofsten)

SELECTION AND MUTATION A *selection* occurs in the cases of many hereditary characters Where hereditary diseases are concerned this selection is generally negative If the term of life is shorter and the fertility less of patients suffering from a hereditary disease we should expect this disease gradually to decrease in frequency, and finally to disappear completely.

Experience shows, however, that many inheritable diseases have occurred for thousands of years at rather unchanged frequencies Chondrodystrophy, for instance, is known from pictures and accounts from the earliest times, and there is reason to suppose that this disease was almost as frequent in Ancient times as it is now The same must be supposed to be the case with haemophilia, which was likewise described by Ancient writers. As, however, the reproductive fitness of both chondrodystrophics and haemophiliacs is very greatly reduced, some factor or other must be present to check the negative selection This factor is no doubt mutation, without which hereditary diseases causing reduced fertility through generations must be expected to become rarer and rarer (comp p 69)

These figures prove the truth of the postulate that in a random mating population the genetic composition of the population is of a constant nature with regard to A and a as long as the allele frequencies p and q remain unchanged. A population in panmixia (a random mating population), in which the 3 genotypes AA, Aa, and aa occur in the proportion of $p^2 : 2pq : q^2$ is *in equilibrium* (Hardy, Weinberg).

Chapter 15

GENETICS OF A HUMAN POPULATION

The future development and genetic composition of a human population are dependent on a variety of factors, hereditary as well as environmental, endogenous as well as exogenous, eugenic as well as euthenic

A very important group of these factors, which determine the fate and survival of a race or a nation, is composed of the hereditary anomalies, abnormalities, defects, and diseases occurring in the population

This is why the study of hereditary diseases plays such a great part in population problems, human genetics, medical statistics, public health, clinical, preventive and social medicine, sociology, and politics. In democratic countries an increasing social consciousness has been manifesting itself, a growing feeling that society must make living conditions tolerable for everybody This has necessitated the study of hereditary diseases, particularly of their frequencies in the population It is of importance that Governmental and Social authorities should know the number of people incapacitated because of hereditary defects, who therefore have to be given social relief, to be treated, or to be placed in hospitals or institutions

A human population is a living body, continuously changing in its composition, variable and inconstant, in progressive or retrogressive development, following the rules of natural selection and evolution, or doing away with these rules, when the "wild type" disappears, as a result of culture and civilisation

Random Mating A *population* consists of genotypically differing individuals. It is a mixture of different biotypes Theoretically a population is supposed to be delimited, not mixing with other populations, and at the same time to consist of an infinite number of persons Furthermore, crossings are

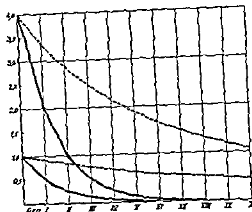


FIG. 27.—Effect of 50 per cent negative selection through 10 generations against the character-carriers with a dominant (————) and a recessive disease (- - - - - -). Initial frequencies 1 per cent and 4 per cent (after v. Hofsten)

character will under identical circumstances only have risen to nearly 0.2 per cent.

Total negative selection of a recessive character does not result in immediate extermination of the character, because the genes will be propagated through heterozygous carriers.

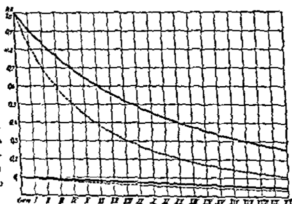


FIG. 28.—Effect of 50 per cent (– – –) and 100 per cent (- - - -) negative selection against the recessive homozygotes with initial frequency 1 and 0.1 per cent through 20 generations (after v. Hofsten)

Total negative selection of a recessive character is rather effective when the character is common, but comparatively much less effective when the character is rare. If, for instance, the character has a frequency of 25 *per cent*, it falls in one generation to about 11 per cent, and after 10 generations to less than 1 per cent. If the initial frequency is 0.1 per cent, it will after 10 *generations* be reduced to only 0.06 per cent, or less than half.

Partial negative selection of a recessive character has a *more* limited effect.

In the cases of certain hereditary diseases the possibility of a positive selection cannot be excluded. It has been maintained, for instance, that mental deficiency has increased in frequency, because mental defectives are supposed to have a greater reproductive fitness than the normal population. This may be true in some instances, but we cannot generalize, because the social conditions vary with time and place.

The effect of selection may result from inhibiting or preventing the propagating of character-bearers of a certain type. The selection may be partial or total. Total negative selection means that the person with the character is entirely prevented from propagation

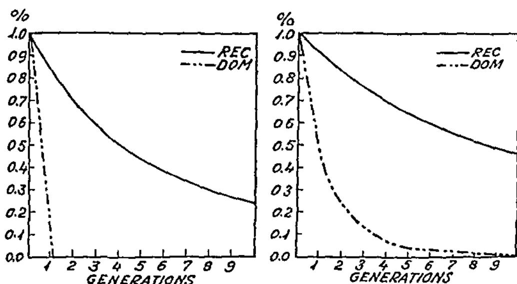


FIG 26—The effect of negative selection against a rare dominant disease (— · · — · ·) and against a recessive disease (————) for 10 successive generations of selection, initial frequency 1 per cent. To the left complete negative selection and to the right 50 per cent negative selection (after Koller mod Stern)

Total negative selection of a dominant character causes instant extermination of the gene. Partial negative selection of a dominant character will reduce the frequency of the character very considerably. If the frequency of the character is, say, 0 1 per cent, and the reproductive rate is half that of the rest of the population, the frequency of the character will after 10 generations be reduced to 0 0001 per cent

Positive selection of a dominant character has a rather strong effect. If the reproductive rate of the character-bearers is double that of the rest of the population, the character will with an initial frequency of 0.1 per cent after 10 generations have risen to 34 per cent of the population A recessive

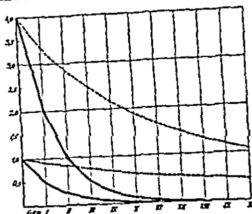


Fig 27 —Effect of 50 per cent negative selection through 10 generations against the character-carriers with a dominant (————) and a recessive disease (------) Initial frequencies 1 per cent and 4 per cent (after v Hofsten)

character will under identical circumstances only have risen to nearly 0 2 per cent

Total negative selection of a recessive character does not result in immediate extermination of the character, because the genes will be propagated through heterozygous carriers

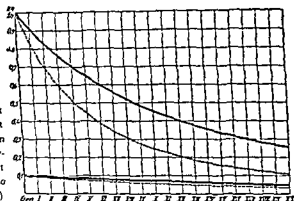


Fig 28 —Effect of 50 per cent (————) and 100 per cent (-------) negative selection against the recessive homozygotes with initial frequency 1 and 0 1 per cent through 20 generations (after v Hofsten)

Total negative selection of a recessive character is rather effective when the character is common, but comparatively much less effective when the character is rare If, for instance, the character has a frequency of 25 per cent, it falls in one generation to about 11 per cent, and after 10 generations to less than 1 per cent If the initial frequency is 0 1 per cent, it will after 10 generations be reduced to only 0 06 per cent, or less than half

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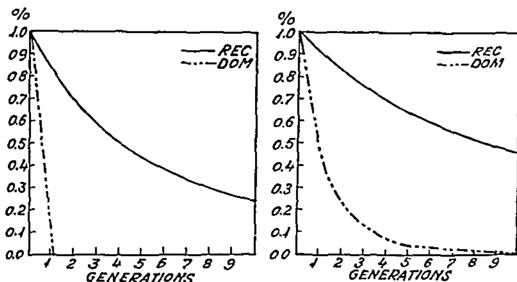


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Positive selection of a dominant character has a rather strong effect. If the reproductive rate of the character-bearers is double that of the rest of the population, the character will with an initial frequency of 0.1 per cent after 10 generations have risen to 34 per cent of the population. A recessive

tions. Total assortative mating is hardly ever seen in human populations, whereas partial is very frequent.

Assortative mating may be positive or negative. There is probably a tendency towards positive assortative mating, e g. as regards body size, superior or inferior intelligence, musical ability, criminality, deafness, blindness, and many other characters.

As examples of negative assortative mating it has been mentioned that a quarrelsome person prefers a peaceable partner, that red-haired persons like partners with another hair colour, and so on. The effect of assortative mating

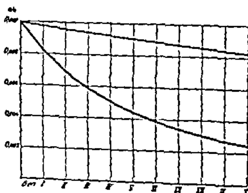


Fig 31—Influence of accumulation in isolates Effect of total elimination of recessive homozygotes through 10 generations, when the population is divided in 10 isolates (- - - - - - -), and in panmixia, i.e. the population is not divided in isolates (————) Initial frequency in the population 0·01 per cent (in the isolates 0·1 *per cent*) (after v. Hofsten)

is generally moderate It has the same consequences as intermarriage, favouring homozygosity

A certain percentage of consanguineous marriages occurs in random mating populations As a matter of fact all marriages are blood marriages even though very distant The term "intermarriage" is only used when more blood marriages occur than are to be expected in panmixia.

A population can be said to consist of partial populations, of isolates, whether geographical or social, in which there is *panmixia*. The size of an isolate influences the frequency of intermarriage

Assortative mating, intermarriage, and isolates are deviations from random mating which cause re-sorting of *the genes in* a population without altering the gene content as do selection and mutation. These mating systems increase the frequency of homozygotes and *reduces that* of heterozygotes, and, therefore, promote the effect of negative selection, thus influencing the balance between negative selection and mutation More recessive mutations become manifest in a population with a high intermarriage frequency than in one with a low

Other factors influencing the genetic composition of human populations,

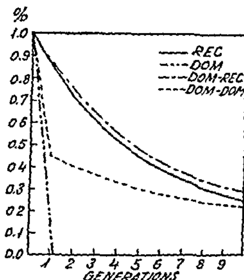


FIG 29—Effect of 100 per cent negative selection for 10 successive generations against 1. a recessive disease, 2 a dominant disease, 3. a disease depending on two factor pairs with dominant genotype in one pair and recessive genotype in the other, and 4 a disease depending on two factor pairs with a dominant genotype in both pairs Initial frequency 1 per cent. The frequencies of the interacting gene pairs are supposed to be alike (after Koller, Zeitschr Konstitl 251, 19, 1936)

If the reproductive rate is, say, 0 5, the frequency will be reduced only from 0.1 to 0 075 per cent after 10 generations.

ASSORTATIVE MATING, INTERMARRIAGE, AND ISOLATES. Assortative mating denotes that individuals prefer conjugal partners of certain genetic constitu-

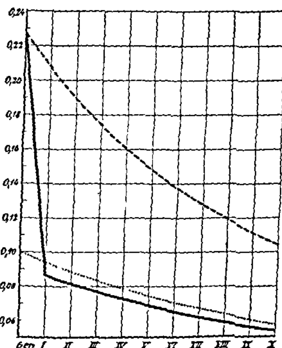


FIG 30—Assortative or nonrandom mating. Effect of elimination through *10 generations* of recessive character carriers (RR) in assortative mating (————) with the intensity of 30 per cent (i e that 60 per cent of the matings between character-carriers and other individuals are not realized), compared with the effect in panmixia (-------). Initial frequency of the disease 0 228 per cent (after v Hofsten)

defect or the disease concerned within a certain group. Conclusions cannot be drawn, however, concerning the incidence of a disease in the population from the results thus obtained, because the mortality generally is higher in affected than in normal individuals. Harelip and cleft palate, for instance, occurs in 0 15 per cent of all new-born infants, whereas the incidence in the total population is only about 0 1 per cent. Within the first year of life alone the mortality for infants with harelip and cleft palate is 25 per cent. Other lesions, e g congenital dislocation of the hip, are not always recognized at birth The incidence is therefore apparently higher in the total population than at birth (*vide* Table 18 p 196)

For the very few hereditary diseases where all or nearly all cases are hospitalized or submitted to special public care direct estimation of the morbidity is, of course, possible without examination of the total population. But if all cases are known of blindness or deaf-mutism, for instance, the difficulty consists in distinguishing between inherited and acquired cases

A very elaborate method for calculating the incidence of hereditary diseases is that of procuring the data, by the aid of birth records, of all persons born, say, 60 years ago within a certain territory to get information on hereditary diseases both in those still alive and also in those who have died, and their ages at death.

The point must be considered that at a group of hereditary diseases only come on within a certain age period, the *period of manifestation* or the risk zone (German· Gefahrdungszeit)

This does not, of course, apply to congenital defects, such as hereditary deformities or oligophrenia But many hereditary diseases, which to all appearance are not congenital, come on within a limited period later in life. Thus, the risk zone for schizophrenia is *generally set between* 21 and 40 (or 16 to 50) years and for manic-depressive psychosis between 21 and 50 (or later) The great majority of the cases of Graves' disease occur between the ages of 20 and 55 Genuine epilepsy usually *first manifests* itself between 5 and 20 Regarding mental deficiency, all individuals who have completed their 10th year of life without displaying signs of this abnormality are regarded as normal in statistical calculations of this kind

By determining the number of individuals within a group presenting a hereditary disease with a limited period of manifestation we get information on the immediate incidence of the disease in the population As a rule it is, however, a matter of greater interest to find the probability of each individual getting the disease if he lives through the whole risk zone, i e to find the *morbid risk* (or the morbidity risk or the expectancy; German: *Krankheitserwartung*) for the disease concerned in the population But in calculating

are, for instance, selective emigration, immigration and deportation, race discrimination, and differential fertility.

The genetic structure of a population and the frequencies of the various hereditary diseases alter in other words, continuously, but the alterations are generally not particularly conspicuous within a limited period.

Genetic drift is the result of chances processes acting during earlier periods when very small isolated populations were forming basis of later larger groups. During the propagation of such extremely small population groups chance loss of some genes or chance fixation of other genes may happen. The effect of this process of genetic "drift" on the genetic composition of a population depends, among other factors, of the population size in populations which were small at one time The variation among different racial groups in frequency of genes determining diseases or of neutral characters as, for instance, blood groups, may partly be due to drift Genetic drift is an evolutionary agent together with mutation and selection.

Morbidity. Many attempts have been made by different methods to estimate the incidence of hereditary defects and diseases in various countries or groups of populations. Some information concerning the incidence of hereditary diseases was obtained centuries ago through vital and medical statistics. Health services are, however, still collecting material for the elucidation of this question

Direct studies of the problem have been carried out for the most part during the last 50 years, originally only on mental defects and diseases but later within the whole field of medicine.

Several methods have been used to investigate morbidity in the average population and to ascertain the amount of hereditary tainting, such as census investigations, sampling methods, and morbidity, mortality, and hospitalisation statistics. These methods may be used in various ways

Sampling methods are often employed in combination with collection and investigation of propositus materials. It must always be considered whether the sample is representative of the average population and fulfils certain requirements with regard to selection and composition.

Census investigations may comprise greater or smaller geographical units, states, counties, municipalities, communities, islands, valleys, etc., or populations delimited according to sex, profession, social class, race, nationality, etc.

Various age groups may be examined, for instance, the new-born, school children, military conscripts, or other age-classes; or mortality statistics may be used

The incidence at birth can be estimated directly only for such hereditary diseases as are easily recognizable in new-born infants, e g grave physical defects This is done simply by counting the number of infants born with the

regions where a medico-genetic or genetic-hygienic registration (vide p 311) has been established, as for instance in Denmark.

Two Danish genetic-psychiatric studies may be mentioned, based on the census method and the sample method respectively, one by Strömgren (1938) and the other by Fremming (1947).

Stromgren took a census of the Danish island of Bornholm (about 40,000 inhabitants), situated in a rather isolated area in the Baltic Sea, relatively close to Sweden. The population of the island is very homogeneous, and there is no intermarriage worth mentioning. Stromgren attempted to count and identify all psychotic, ex-psychotic, or mentally defective persons living on the island at a certain date Furthermore, Stromgren took a more thorough census of a small district of Bornholm, inhabited by about 1000 persons, where adequate information was easily obtained about each individual.

Fremming carried out an investigation using the sample method originally suggested by Klemperer. Fremming's basic material of propositi consisted of the persons born on Bornholm within the five-year-period 1883-7, somewhat more than 5,500 persons More than 92 per cent of the propositi, most of them over 55 years of age, were traced and examined The frequencies of psychoses, psychopathy, oligophrenia, epilepsy, criminality, tuberculosis, and some other diseases were calculated, and a thorough demographic analysis of the material was performed

Tables 18-21 are based chiefly on the results obtained by the two above-mentioned investigations and the material collected in the medico-genetic register of the Copenhagen Institute for Human Genetics

GENE FREQUENCY Direct conclusions cannot be drawn concerning the *frequency of the corresponding* gene in the population from a knowledge of the incidence of a hereditary disease But this can be calculated from the morbidity, if we know the *mode of* transmission of the disease and the penetrance of the gene, on the assumption of random mating

If we call a dominant gene D and the recessive allelomorph R, and if the gametes containing D and R respectively occur at the frequencies d and r ($d + r = 1$), we know as follows:

Dominant homozygotes DD	occur at a frequency of d^2
Heterozygotes RD	" " " " " $2\,dr$
Recessive homozygotes RR	" " " " " r^2
Dominant character RD + DD	occurs " " " " $2\,dr + d^2 = 1 - r^2$

Frequency of RR in per cent $= r^2 \cdot 100$, $r = \sqrt{RR} \cdot 10$

" " DR " " " $= 2\,dr \cdot 100 = 20\,\sqrt{RR} - 2\,RR$

" " DD " " " $= d^2 \cdot 100 = 100 - 20\,\sqrt{RR} + RR$

the morbid risk consideration must be taken both of the age at onset of the disease and the age distribution in the group examined. In the individuals who have not yet reached the risk zone all have full chance of getting the disease later in life. Those who are in the midst of the manifestation period have a certain, though smaller chance of getting the disease, decreasing with increasing age; and only for those who are old enough to have passed the entire risk zone is the morbid risk *nil*.

The morbid risk of schizophrenia in a group of 4000 individuals, of whom 1000 under 20 years of age, 2000 between 20 and 40, and 1000 over 40, and where 7 between 20 and 40 and 7 over 40 have the disease, is not 14 · 4000 = 0.35 per cent, but higher We cannot calculate the morbid risk in proportion to the total number of individuals in the group, but must use a *reduced proportional* (German: Bezugsziffer). The 1000 under 20 years of age still have a full chance of developing schizophrenia, so they cannot be included among the non-schizophrenic. The 2000 between 20 and 40 can still get the disease. The chance is roughly 50 per cent for the whole group (according to Weinberg's simplified method). They can therefore in the proportional be reckoned only as ½ × 2000 = 1000 individuals with no risk. Only the 1000 over 40 years of age can be regarded as definitely non-schizophrenic. Hence they must all be included in the reduced proportional. The morbid risk for schizophrenia in the group concerned is then 14 · 2000 = 0 7 per cent. But we cannot draw direct conclusions from this figure concerning the number of schizophrenics in the population at a given point of time This is much lower than 0.7 per cent, presumably about 0 2 to 0 3 per cent

It has been stated that the chance of developing schizophrenia can be set at 50 per cent for the total number of persons between 20 and 40, the age period of manifestation. This is an approximate value only, for it requires that the times of onset are fairly equally distributed over the whole manifestation period and that the affected have the same mortality as normals. These requirements are not fulfilled, however. A more exact method has therefore been elaborated for estimation of the "Weights" of the individual persons within the manifestation period by making independent calculations of this for each one-year, five-year, or ten-year period within the risk zone.

If the morbid risk of schizophrenia is calculated at about 0 7 per cent, 70 out of 10,000 new-born should get the disease if they lived long enough to pass through the whole risk zone But some of these predisposed individuals die before the onset of the disease By following up 10,000 individuals born 50 years ago we do not find as many as 70 schizophrenics among those still alive. The number found depends not only on the mortality in the population concerned, but also on that of schizophrenics, which is considerably higher than the death rate in the average population.

During recent years new possibilities have been created for investigations on the frequency of hereditary diseases in the population, in countries or

regions where a medico-genetic or genetic-hygienic registration (*vide* p. 311) has been established, as for instance in Denmark.

Two Danish genetic-psychiatric studies may be mentioned, based on the census method and the sample method respectively, one by Strömgren (1938) and the other by Fremming (1947).

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Gene Frequency Direct conclusions cannot be drawn concerning the frequency of the corresponding gene in the population *from a knowledge of the* incidence of a hereditary disease But this can be calculated from the morbidity, if we know the mode of transmission of the disease and the penetrance of the gene, on the assumption of random mating

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Frequency of RR in per cent $= r^2 \cdot 100$, $r = \sqrt{RR} \cdot 10$

" " DR " " " $= 2\,dr \cdot 100 = 20\sqrt{RR} - 2\,RR$

" " DD " " " $= d^2 \cdot 100 = 100 - 20\sqrt{RR} + RR$

The percentage frequencies of DR and DD can be calculated from the 2 latter formulae, if we know the percentage frequency of RR.

Table 2 can be calculated by means of this formula

The relation between heterozygotes RD and recessive homozygotes RR is

$$\frac{RD}{RR} = \frac{2rd}{r^2} = \frac{2(1-r)}{r}$$

If those having the recessive character are very few, then the heterozygotes will be proportionally very common If the frequency of a recessive disease, for instance, is 0.1 per cent, then, as the Table shows, 6.12 per cent of the population must be heterozygotes; and if the frequency is 1 per cent, 18 per cent are heterozygotes.

It appears further from Table 2 that dominant diseases nearly always occur in the heterozygous form If the frequency of a dominant disease is 1 per cent, which is relatively high, it is present in the homozygous form in only 1 out of about 40,000 cases In cases of rarer dominant diseases the homozygous form is still more exceptional. These calculations apply, however, only on the assumption of random mating, which hardly ever occurs in human populations

TABLE 2

	Recessive homozygotes	Heterozygotes	Dominant homozygotes	Individuals w dominant character
Zygotes	RR	DR	DD	RD + DD
Frequency	r^2	2dr	d^2	$1 - r^2$
	%	%	%	%
	0 001	0 63	99 369	99 999
	0 01	1 98	98 01	99.99
	0 1	6 12	93 78	99 9
	1	18	81	99
	4	32	64	96
	10	43 2	46 8	90
	16	48	36	84
	25	50	25	75
	50	41 4	8 6	50
	80	18 9	1 1	20
	99	1	0 000025	1

CHAPTER 16

METHODS OF MEDICAL GENETICS

The question whether a disease is hereditary and how it is inherited can often be answered by a simple study of a few pedigrees. If the disease occurs without skipping through several generations and in about half of the offspring of the affected individuals, it is likely to be a dominant disease. More scattered occurrence in the families, particularly where intermarriage is present, and manifestation in on an average 25 per cent of the siblings of the affected, suggest recessive inheritance. If the disease is most frequent in males and is inherited through the unaffected daughters of affected males the inheritance must be supposed to be of a sex-linked recessive nature. The conditions are often less conspicuous, however, necessitating special methods for clarification of the hereditary transmission. The inheritance of a disease can be analysed by *statistic-genealogical methods* and the *twin method* serves to elucidate whether a disease is hereditary and to determine the frequency of manifestation of the pathogenetic gene concerned

Population genetics is concerned with the study of the genetic composition of whole populations Medical genetics sensu striction includes twin investigations and pedigree genetics, the analysis of the individual family and statistical evaluation of collections of pedigrees

STATISTIC-GENEALOGICAL METHODS After having collected information on a large number of families for the purpose of studying the inheritance of a disease we must submit the material collected to a statistical analysis. The collection starts from a number of propositi, often several hundreds, who all have the disease concerned *This is called the propositus method* or the *proband method* The investigation may comprise a greater or smaller number of family groups, always parents and siblings of the propositus, and, if possible, also his offspring and the offspring of his siblings, often also grandparents, parents' siblings, and possibly the offspring of the latter For each family group included reliable data *must* be procured concerning all members of the group, including the healthy individuals, and their ages, (possibly age at death) in order to be able to indicate the frequency of the disease, or the morbid risk, in the group in question In cases of non-congenital diseases an age correction has to be made, as mentioned p 119

In calculating the morbid risk for family group with many young members we must pay attention to the fact that the age correction involves a possibility of a considerable error If, for instance, we calculate the morbid

risk for the offspring of manic-depressive patients at 25 per cent, this group may comprise many who have not yet reached, or passed through the manifestation period, and who therefore should not be included in the calculation of the reduced proportional. Even a few manic-depressive in this group may then easily convey the impression of a relatively high morbid risk.

By the propositus method care must be taken that the propositi are not *selected* in a biased way, but are *representative* of all patients with the disease concerned in the population. By using hospital patients, for instance, we shall probably get a preponderance of severe cases, and if we collect the propositi exclusively from an urban population, we cannot be sure that they are representative of the whole country. The propositi must be chosen without regard to a hereditary taint in the family. If not, the investigation will often show too great a taint, as attention is attracted particularly towards patients belonging to families with marked hereditary predispositions Many pedigrees owe their publication to peculiarities in the number or symptoms of affected individuals; they are selected for "oddity-interest". The ordinary cases are, however, as important as the conspicuous ones; to leave some of them out will be a source of bias in the pooled data from many families.

After having collected the material we may proceed by 2 routes, which, however, in reality do not differ much from each other. We may either *a priori* form a preliminary estimate of the mode of transmission, and then investigate whether the figures found are in agreement with this estimate Or we may first look at the distribution of the disease in the various groups of relatives and then *a posteriori* draw conclusions concerning the hereditary transmission. But no matter whether one or the other procedure is employed we must compare the figures found with those expected according to one or the other mode of transmission, by using special methods for correcting ratios from the pooled data

Formulae have been found for calculating the frequencies to be expected in a disease in the different groups of relatives at dominant and recessive inheritance respectively and at different frequencies of the disease in the population Tables have been made on the basis of the formulae Tables 3 and 4 are extracts of such. (After Dahlberg & Hultkrantz)

In the Tables the dominant gene is termed D and the corresponding recessive gene R, while d denotes the frequency of gametes containing D and r that of gametes containing R

The so-called *sib method* may be regarded as a greatly simplified propositus method. Both methods were originally elaborated by Weinberg and have since been improved by various writers By the sib method we examine only the siblings of a number of propositi with a certain disease and calculate the

frequency of the disease among them. In case of recessivity we should then expect to find nearly 25 per cent affected siblings (the ideal ratio 3:1) and in case of dominance about 50 per cent (the ideal ratio 1:1). There are, however, two sources of error: 1) If the propositi are counted in, this would give too high values. Then each sibship would contain at least one affected, the propositus, and in several cases it will consist of only one or very few children. If the number of children in a given family is only 2, one of them (50 per cent) or both (100 per cent) will be affected. If the material is chiefly made up of families with one, two, or three children, it will show an additional surplus of affected children in proportion to the unaffected ones. 2) In cases of small sibships where the first and possibly also the second and the third child are unaffected, these sibships may evade detection, in spite of heterozygosity in the parents.

The sib method has been used to correct these two sources of error. According to this method the affected and unaffected siblings of the propositi are counted, whereas the propositi themselves are excluded. Each sibship is counted in as many times as there are affected siblings, i.e. each patient is regarded once as propositus and as such not included in the counts. If the material is not selected the ratio of affected to total number of siblings is 1:1 for dominant diseases and 1:3 for recessive.

TABLE 3

Frequency of a recessive disease (RR)

in the population	in the following groups of relatives of affected			
	siblings	parents and offspring	grandparents grandchildren and parents siblings	great grandparents great grandchildren and offspring of parents siblings
r^2	$\frac{(1+r)^2}{4}$	r	$\frac{r(1+r)}{2}$	$\frac{r(1+3r)}{4}$
%	%	%	%	%
0	25	0	0	0
0.1	26.60	3.16	1.63	0.86
0.5	28.67	7.07	3.79	2.14
1	30.25	10	5.50	3.25
10	43.31	31.62	20.81	15.41

Using the *a priori* propositus method for brothers and sisters only, the affected and unaffected siblings of the propositi are counted, but only one propositus is counted *in each* sibship and the propositi themselves are not included in the counts. As regards recessive diseases the ratio of affected to

total number of siblings of the propositi is *a priori* supposed to be 1:3. If the material is not selected, the affected will, however, constitute only between 14 and 18 per cent depending on the number of siblings in each sibship.

TABLE 4

Frequency of a dominant disease (RD, DD)

in the population	in the following groups of relatives of affected			
	siblings	parents and offspring	grandparents grandchildren and parents siblings	great grandparents great grandchildren and offspring of parents' siblings
$1 - r^2$	$1 - \frac{r^2(3+r)}{4(1+r)}$	$1 - \frac{r^2}{1+r}$	$1 - \frac{r^2(2+r)}{2(1+r)}$	$1 - \frac{r^2(4+3r)}{4(1+r)}$
%	%	%	%	%
0	50	50	25	12.5
0.1	50.04	50.04	25.07	12.58
0.5	50.21	50.18	25.34	12.92
1	50.44	50.38	25.69	13.34
10	54.41	53.82	31.91	20.96

In case of a dominant disease the sib method gives equally many affected and unaffected siblings of the propositi, while the *a priori* propositus method gives 30 to 40 per cent affected siblings.

Both methods are based on unselected material and complete information on each sibship. Selection may be due to the fact that familial occurrence is sooner recognized and published than solitary cases.

Using a different method of ascertainment the 3:1 ratio for recessive diseases may also be expected from the pooling of sibships. If the pooled sibships are children of parents who have been ascertained to be heterozygous, by other information than that obtained by the presence of affected children, then all possible sibships will be noted, including those in which *none* of the children are affected.

The figures found by the propositus method in the various groups of relatives can, of course, be compared with corresponding figures from the same age-classes in the normal population. Such control calculations have previously been mentioned (p. 118).

Statistic-genealogical methods can be employed only for hereditary diseases constituting a genetic entity. Whether this is the case can be estimated by studying how the disease is distributed in the various propositus families. Furthermore it is necessary to know the frequency of manifestation of the

gene concerned If this is not 100 per cent, we must expect a correspondingly lower morbidity in the various groups of relatives

There are many special problems attached to the propositus method of investigation. It is, for instance, a matter of importance to know details about the occupations and social standards of the propositi and their affected relatives, as well as whether they live in rural or urban districts. The effective fertility and average longevity of the affected is also of interest, as well as the manifestation period of the disease; further, the question of a possible correlation between the hereditary diseases occurring in the families, e g. whether senile dementia is particularly frequent among the parents of schizophrenics, whether there is a relationship between psychopathy and intelligence, and which kinds of psychosis are particularly associated with paranoia among the relatives

The statistic-genealogical methods often have to be combined with a study of the pedigrees themselves. Thus, for instance, the possibility of the onset of a disease by mutation with ensuing dominant inheritance, low reproductive rate in the patients and extinction of the disease in the course of a few generations is easier to investigate by a combination of pedigree studies and statistic-genealogical methods than by the latter methods alone.

THE TWIN METHOD In cases of dominant diseases, and often also of recessive if the gene shows full manifestation, inheritance can be demonstrated exclusively by statistic-genealogical methods But where the conditions are less simple twin studies must be included.

The external circumstances under which the individual twin sibs of a same-sexed two-egg pair and a one-egg pair grow up are generally speaking relatively uniform under normal social conditions, provided one twin does not suffer from a severe hereditary or acquired defect. Later in life the environments of two-egg twins will as a rule differ more than those of one-egg twins, because the similarity of the latter with regard to their emotional nature and powers inclines them to seek the same type of occupation and the same associates more than is the case with two-egg twins All the same we may say that, supposing there are no defects, same-sexed pairs of twins will grow up in as similar external conditions as can be found in human society.

As previously stated, one-egg twins must in the main be supposed to possess the same hereditary factors, whereas two-egg twins genotypically show no greater resemblance than do other siblings This fact is utilized in the study of the dependence of a given disease on hereditary factors, if one wants to assess the peristatic variation of manifestation

To investigate by means of the twin method whether a hereditary disease



Fig 32—*Spina bifida umbalis in one-egg twins (after Eskelund and Bartels)*

or abnormality depends on hereditary factors we must, as already stated, *in the main proceed as follows*. *We must examine the twin sibs of a one-egg* pair to see whether the disease concerned is concordant or discordant, and at the same time, *for the sake of control, we must make a similar examination* of two-egg pairs of twins If the disease is obviously hereditary and the gene presents a high frequency of manifestation the disease will always show concordance in one-egg twins. *If the development of the disease depends to some* extent on environmental factors, we may occasionally find discordance, and *if it is not hereditary discordance is just as frequent in one-egg as in two-egg* twins. In Table 5 examples of twin investigations are stated

The question of heredity in a given disease can be settled by means of the twin method combined with the statistic-genealogical method

By both methods we can make out whether a disease is hereditary or not. By the former it is also possible to demonstrate whether the gene shows full manifestation or, *if not, to measure the power of manifestation*, but *nothing* can be found out with regard to the mode of transmission *By the latter method the figures arrived at give some idea of the hereditary transmission and perhaps* also of the frequency of manifestation. *Both methods combined should give* full information on the genetic conditions

By a twin study *there are, however, various special facts to be considered*

The material must not be selected. The question of concordance with regard to, say, mental deficiency cannot be investigated by selecting in a mental hospital all the patients who are known to be twins, and procuring the data of their twin sibs, as this would give far too great a concordance. In the

TABLE 5

Various Twin Investigations.

	One-egg twin pairs		Two-egg twin pairs	
	Number of pairs investigated	concordance ++	Number of pairs investigated	concordance ++
Feeblemindedness (*vide* p 279)				
After J C. Smith (Denmark, 1929)	16	88 %	50	8 %
After Rosanoff *et al.* (U S A, 1937)	126	91 %	93	45 %
Manic-depressive insanity (*vide* p. 288)				
After Luxenburger (Germany, 1937)	33	94 %	17	6 %
After Rosanoff *et al* (U S A, 1935)	23	70 %	67	16 %
Schizophrenia (*vide* p 285)				
After Luxenburger (Germany, 1937)	21	67 %	37	0 %
After Rosanoff *et al* (U.S A, 1934)	41	68 %	53	19 %
Epilepsy (including all types of seizures)				
After Conrad (Germany, 1936)				
Symptomatic	8	13 %	34	0 %
Cryptogenetic	22	86 %	93	4 %
After Lennox (U S A, 1951)				
With prior brain damage	24	17 %	13	8 %
Without prior brain damage	45	84 %	40	10 %
Criminality (*vide* p 293)				
After Lange (Repeated offenders) (Germany, 1929)	13	77 %	17	12 %
After Kranz (chiefly first time off) (Germany, 1936)	31	65 %	43	54 %
After Rosanoff *et al.* (U S A, 1941)	45	78 %	27	22 %
Total of several investigations	111	72 %	111	34 %
Clubfoot (*vide* p 204)				
After Idelberger (Germany, 1938)	35	23 %	133	2 %

hospitals it is often not noticed whether a patient is a twin unless the other twin has the same disease or has been admitted to the same hospital. The incidence of concordance proves to be much lower when the number of twins among the patients admitted to the hospital concerned is found out by reviewing the birth registers, and information afterwards procured on possible diseases in the twin sibs

The most correct result is achieved by working with a fairly large entirely



Fig. 33.—Vitiligo in one-egg twins. Concordance with quantitative differences (after J. Mohr).

unselected series of twins, whose data are collected no matter whether the twins are ill or not Some of these twins are ill, and an investigation is now carried out to see whether their twin sibs likewise are affected. If the series is sufficiently large it may serve as a basis for a correct assessment of the incidence of concordance of a number of diseases Most diseases being rare, however, the series of twin pairs required would have to be so large that it is practically impossible to procure. In a population group including one million inhabitants only between 200 and 300 pairs of twins are born each year, of whom about 50-100 pairs are identical According to Rife more than one and a half million pairs of twins are living in the United States, and about a third of them are monozygotic

In addition, procuring of a large number of twin pairs with both partners *alive is rendered difficult by the fact that twins have a relatively short lifetime.*

Weinberg has made the following calculation on the basis of the conditions in Germany Of all infants born only about 70 per cent live to the age of 20 The life of twins is so much shorter that the ratio of twins to normals who reach the age of 20 is about 70 to 100.Out of 80 births 1 is a twin birth Of the 78 single children 78 × 0 7 = 54 6 will live to the age of 20. For twin sibs the chance of reaching the age of 20 is 2 × 0 7 × 0 7 = about 1. This means that among 54 6 + 1 = about 56 persons aged 20 there is on an average 1 twin The infant mortality varies, of course, somewhat from place to place and from time to time, but, owing to the pre- and postnatal lethal selection, we must no doubt in general reckon that less than 2 per cent of the total population are twins To this may be added that one-egg twins have a higher mortality than two-egg twins Adult one-egg pairs with both twins alive are therefore rarer than might be expected Moreover, many diseases reduce the longevity and thereby also the frequency of adult one-egg twin pairs suffering from such diseases.

All these facts naturally add to the difficulty of procuring a sufficiently large number of unselected one-egg pairs of twins with a certain disease. So in the cases of comparatively rare diseases we must for the time being renounce the strict requirements of an entirely unselected twin series and base our calculations partially on casuistic reports. Doctors who observe rare diseases which may be hereditary in one-egg twins ought therefore always, no matter whether the disease is concordant or discordant, take care that their observation becomes universally known, either by publishing it or by sending a report on the case to a scientific central institution[1].

In hereditary diseases we must, because they are hereditary, reckon with a certain concordance also in two-egg twins. If the probability of occurrence of a hereditary disease in a sibship is p, then the probability that two-egg twin pairs in which one twin has the disease show concordance is $\frac{100\ p}{2-p}$. In dominant diseases with full manifestation, if one parent has the disease, this probability is 33 per cent, in recessive diseases, if both parents are carriers, 14.3 per cent. By mere coincidence twin pairs occasionally show concordance with regard to a character, whether hereditary or not, particularly, of course in cases of frequently occurring characters. The incidence of such concordance can be calculated in the following way: If a disease, e.g. one of the ordinary infectious diseases, has occurred at least once in 40 per cent (= a) of all people, then 60 per cent (= b) have not had the disease. How often the disease happens to be concordant or discordant or not to have occurred at all, in 2 persons chosen at random from the population appears from the individual results achieved by calculating $(a + b)^2$:

a^2 pairs = 16 per cent show concordance with regard to the disease
$2ab$ „ = 48 „ „ „ discordance „ „ „ „ „
b^2 „ = 36 „ „ „ concordance „ „ „ not having had the disease

If we include only the pairs with at least one affected twin, the ratio of concordant to discordant pairs becomes $a^2 : 2ab$, in the stated instances 1:3.

If 10 per cent of the population have had the disease: $a^2 : 2ab = 1 : 18$
„ 1 „ „ „ „ „ „ „ „ „ $a^2 : 2ab = 1 : 198$
„ 0.1 „ „ „ „ „ „ „ „ „ $a^2 : 2ab = 1 : 1998$

This frequency of concordance is due exclusively to coincidence. It must be equally high in one-egg and two-egg twins. However, in the cases of rare diseases it is of little practical importance.

[1] The *International Bureau of Human Genetics*, Tagensvej 14, Copenhagen, N Denmark (affiliated to the Section of Human Genetics of IUBS and UNESCO) is collecting material concerning the inheritance of rare diseases and twin observations



FIG 33 —Vitiligo in one-egg twins. *Concordance with quantitative differences* (after J Mohr)

unselected series of twins, whose data are collected no matter whether the twins are ill or not Some of these twins are ill, and an investigation is now carried out to see whether their twin sibs likewise are affected. If the series is sufficiently large it may serve as a basis for a correct assessment of the incidence of concordance of a number of diseases. Most diseases being rare, however, the series of twin pairs required would have to be so large that it is practically impossible to procure. In a population group including one million inhabitants only between 200 and 300 pairs of twins are born each year, of whom about 50-100 pairs are identical According to Rife more than one and a half million pairs of twins are living in the United States, and about a third of them are monozygotic

In addition, procuring of a large number of twin pairs with both partners alive is rendered difficult by the fact that twins have a relatively short lifetime.

Weinberg has made the following calculation on the basis of the conditions in Germany. Of all infants born only about 70 per cent live to the age of 20. The life of twins is so much shorter that the ratio of twins to normals who reach the age of 20 is about 70 to 100. Out of 80 births 1 is a twin birth Of the 78 single children 78 × 0 7 = 54 6 will live to the age of 20 For twin sibs the chance of reaching the age of 20 is 2 × 0 7 × 0 7 = about 1. This means that among 54 6 + 1 = about 56 persons aged 20 there is on an average 1 twin. The infant mortality varies, of course, somewhat from place to place and from time to time, but, owing to the pre- and postnatal lethal selection, we must no doubt in general reckon that less than 2 per cent of the total population are twins To this may be added that one-egg twins have a higher mortality than two-egg twins Adult one-egg pairs with both twins alive are therefore rarer than might be expected Moreover, many diseases reduce the longevity and thereby also the frequency of adult one-egg twin pairs suffering from such diseases

Twins as a rule grow up and are reared together, in other words under almost the same external conditions. Their roads do not part until adulthood. It does happen, however, though extremely rarely, that twin sibs are separated from each other immediately after birth to grow up under widely different circumstances. Newman *et al.* in Chicago procured a series of such twins grown up in different environments Such a series naturally affords a particularly favourable chance of studying the importance of paratypic factors for the development during childhood and adolescence. Investigation of such *twins reared apart* shows that heredity plays an important part in the determination of the I Q differences between two-egg twins. Studies of intelligence-test behaviour indicate high similarity in intelligence quotient of one-egg twins whether raised together or apart. Tests on temperament and emotional behaviour gave less conformity in one-egg twins than the I Q tests. Still, a considerable likeness in basic personality traits is obviously present between one-egg twins reared apart

In twin studies concerned with a disease, a close analysis of the discordant one-egg twin pairs is often of importance for an understanding of the pathogenesis By studying twins with a view to mental affections, for instance, such as mental deficiency, or criminality, the affected twin of a discordant one-egg pair will often, by questioning or examination, be found to have had an exogenous brain lesion, meningitis, encephalitis, or the like, which has caused a permanent damage of the brain accounting for the discordance

The heritability of a trait in dizygotic twins may be estimated by the formula: $H = \frac{C_M - C_D}{100 - C_D}$, where C_M represent the percentage of concordance in monozygotic and C_D in dizygotic twins. In feeblemindedness (vide table 5), for instance, C_M is found to be 91 per cent and C_D 45 per cent. According to the formula H can then be calculated to about 84 per cent, i.e. about 84 per cent of the intra-pair variations in dizygotic twins in respect to feeblemindedness may be ascribed to differences in heredity.

Finally, in assessing the result of a twin study we must also take into consideration the fact that the difference between one-egg and two-egg twins is greater in a heterogeneous than in a homogeneous population. In a homogeneous population there is a relatively small difference between two-egg twins, because they possess to a great extent the same hereditary factors. Thus, we cannot say categorically that the same frequency of concordance in one-egg and two-egg pairs militates against the inheritableness of a property. We may also, at least theoretically, regard it as indicative that the population concerned, is very homogeneous in a genetic respect.

The significance of paratypic factors in relation to that of idiotypic factors for the development of a property can be analysed by a twin study, where the twin pairs are divided into 3 groups:

1. Hereditary and environmental factors are alike.
2. Hereditary factors are alike, environmental factors differ
3. Hereditary factors differ, environmental factors are alike

In this way v. Verschuer claimed to be able to calculate the relation between environmental and genetic influences as follows: for body weight: 1.2, for breast width. 1:2.4, for body height: 1·10.4, and for head length 1:5.6

Newman, Freeman, and Holzinger observed an intrapair correlation in stature of $r_M = +0.9$ in monozygotic twins and of $r_D = +0.5$ in dizygotic twins, r indicates the coefficient of correlation. The intrapair-variation dependent on heredity in dizygotic twins in respect to body height may then be calculated to $H_D = \frac{r_M - r_D}{1 - r_D} = \frac{0.9 - 0.5}{1 - 0.5}$ which is 80 per cent.

Regarding diseases a distinction has been made between those showing great peristatic instability and those showing great peristatic stability, or if you like, those with a considerable and those with a limited reactivity to environmental influence. Theoretically their dependence on hereditary factors varies between 0 and 100 per cent, but in practice it never reaches either of these extremes. The peristatic variability changes throughout life, and is often different in the 2 sexes.

meric genes present in the homozygous form in several chromosome pairs (Ø Winge) All varieties or races within the species thus contain numerous homozygous identical "species genes", while their mutual differences are due to a much smaller number of "racial genes", which by race mixture are segregated according to Mendelian laws

As a mixture of species is rather rare we have no opportunity of studying segregation of the species genes by this means. By mutation, however, heterozygosity for species genes may arise, which can be identified and localized in the chromosomes of animals, where crossing experiments are possible. In the fruit fly, for instance, the genes for a great number of normal traits characterizing it as a species have been localized in this way. This is the case with such traits as shape of body, size, shape of wings, colour of body and eyes, etc

There must be supposed to exist species characters so important that the *individual* is destroyed if they mutate. Such species characters are therefore constantly preserved. There is presumably a gradual transition from mutated genes, which are absolutely lethal, through dominant genes with a recessive lethal effect to sublethal genes

Genes are also found which are common to groups *superior to the species*, *e g* the genus, which comprises several species. Such genes determine the development of characters which are found unchanged within the various animal species

Some of the normal traits are so stable that they do not vary at all within the species, and they are, as a rule, due to polymeric genes Our knowledge of their heredity is therefore limited In the following the normal traits will only be briefly described, *chiefly* in as far as they are of practical importance in medical science in connection with blood transfusion, determination of paternity, the polysymptomatic similarity test, and with investigation of constitutional types

Chapter 18

MORPHOLOGICAL TRAITS

Anthropometry Anthropometric methods are required for the study of the ways in which morphological traits in man vary from individual to individual. The individual measurements are determined quantitatively by means of instruments constructed specially for the purpose, such as caliper compasses, rulers,

Part III

NORMAL HEREDITARY FACTORS IN MAN

CHAPTER 17

OCCURRENCE AND DEVELOPMENT OF NORMAL TRAITS

The genes must from the outset be supposed to act as a kind of regulating factors determining the evolution of the fertilized egg through the early embryonic stages as well as later on. We do not know whether the inductors and organisers demonstrated by Spemann, which control early development, can be associated with certain genes. But the morphological and physiological development and growth of the entire organism, as well as its individual parts and functions are regulated by genes This appears from numerous investigations, which have been carried out into normal traits in twins, as well as into hereditary characters which vary within the species. are pathological, or otherwise differ from the norm The effect of a gene can be demonstrated only if 2 individuals, differing with regard to the gene concerned and the character it produces, are crossed, and propagation takes place

Normal growth and the entire developmental rate must depend on genes, as we know of recessive and dominant genes which produce dwarfism, beginning either prenatally (primordial dwarfism, chondrodystrophy) or in infancy (infantile dwarfism), or possibly combined with metabolic disturbances (adiposogenital dystrophy) Each pathogenetic gene must have a normal allelomorph In all the human organs and functions we have come to know genetically determined conditions which show that their normal development also must depend on hereditary factors

Traits that are common to all humans, the species characters of man, are presumably due to hereditary units present in the homozygous form in all individuals of the species, so that segregation of genes for species characters are not observed by crossing of individuals belonging to the species There is reason to suppose that the particularly stable characters are due to poly-

helical, and it may be more or less coarse. There is found one gene for curly hair and one for helical, which both dominate over that for smooth hair. The straight hair seen in Mongols dominates over all other forms.

There is some disagreement as to the whorling of the hair on the crown of the head Some writers believe that a clockwise whorl dominates over a counter-clockwise whorl, and that mirror imaging is frequent in one-egg twins, where then the whorl is clockwise in one and counter-clockwise in the other Others are of the opinion that the whorl direction depends chiefly on an intra-uterine environmental influence.

Iris pigmentation depends on several genes, some pigment-producing, and some pigment-distributing In light eyes the pigment is localized in the posterior layer of pigmented epithelium, while in dark eyes it is also distributed over the anterior layers The inner layer is always pigmented except in albinos The colour of the eye depends, however, not only on the pigment, but also on the opacity and structure of the frontal boundary layer. The eyes poor in pigment may therefore vary from light blue through steel grey to dark grey The development of the frontal boundary layer of the iris is hereditary, and it does not extend quite to the edge of the pupil. When describing the iris we must therefore distinguish between an inner and an outer zone, which often differ somewhat in colours. Central, as well as diffuse, atrophy of the frontal boundary layer may be seen. This layer may further present a [illegible]

Di [illegible]

of [illegible] effects of laying and zoning Definitely blue eyes are generally recessive to green and light brown, which again are recessive to dark brown There are exceptions to this rule, however. Blue-eyed parents have been seen to have a brown-eyed child. Probably the blue eye has originated several times during the generations as a mutation from the original brown

The eyes of females are generally somewhat darker than those of males. Eskelund has shown that the number of contraction furrows is hereditary, as are also the central and the diffuse atrophy of the frontal boundary layer. The same is the case with the width of the cornea; a large width is dominant to a small one

One-egg twins show extremely great concordance with regard to both eye colour, iris structure, number of contraction furrows, and atrophy of the frontal boundary layer

Brown is the commonest eye colour in man with a minor incidence of mixed and light The so-called black eyes are produced by a dense deposit

slide-gauge, balances, and special cameras. Estimations of the qualitatively varying traits, on the other hand, such as colour of eyes, form and colour of hair, etc., is based on special colour and other test scales. Often it is not the *absolute measurements one is interested in comparing, but their correlation* which may be expressed in indices. One may also use empirically elaborated standard tables indicating the normal proportions of these measures in the 2 sexes and in different age-classes.

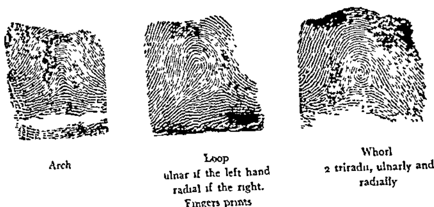
PIGMENTATION, HAIR, AND IRIS STRUCTURE. There is a certain, though by no means consistent correlation between the pigmentations of skin, hair, and iris (complexion). Hence there is reason to suppose that superior genes exist which are responsible for all production of pigment

Skin colour depends on polymeric genes, possibly on *multiple allelomorphs.* Dark skin colour seems to dominate over fair The yellow skin colour of the Mongols also dominates over the European white

The production of irradiated ergosterol is facilitated by a fair skin. The mutation to blondism with fair skin reaches a high frequency in cool, damp, and cloudy regions, the countries where pale-skinned people are common, but albinos are also seen occasionally among Negroes, Arabs, Indians and in fact everywhere.

The genetic conditions of *hair colour* have been thoroughly investigated on a number of mammals, from which an analogy has been drawn to man. There is supposed to exists a basic factor for pigmentation in general. Absence of this results in albinism Further, a special distribution factor is found, as well as 2 factors for brown and black pigment respectively Finally, there exists an independent gene for red hair. Each of these factors are be*lieved to consist of a series of multiple allelomorphs differing in degree* The size and number of melanin granules determine hair colour from blonde to black; and furthermore a red pigment is also involved Blond hair is originally presumed to result from loss of one or more genes for dark hair colour. Dark hair colour dominates over blonde, but 2 blonde parents are nevertheless occasionally seen to have a dark-haired child The new-born infant often has dark hair, possibly owing to hormonal influence from the mother. This hair falls out during the first few months of life, and the next growing out is generally fairer, but is subject to a certain darkening later in life. The colour of the hair depends not only on the pigment, but also on the refraction in the cuticular epithelium, the contents of air-bubbles, and the fat content.

Hair Form may vary from straight or smooth through wavy to curly or



Arch

Loop
ulnar if the left hand
radial if the right.
Fingers prints

Whorl
2 triradii, ulnarly and
radially

Fig 35



Fig. 36 —2 finger prints, with loop, with few and many ridges respectively between triradius and midline of loop

between 2 transverse lines A triradius is formed where these lines part. Whorl formation with a larger or smaller number of concentric rings gives 2 triradii The same is the case with double loops By connecting the triradial point with the point of core of the whorl or the loop we cut off a certain number of ridges, which we can count and thereby obtain a quantitative expression of the pattern

Kristine Bonnevie has made embryological investigations into the development of the cutaneous ridges The results of these, compared with those of family studies, have led to a theory concerning the inheritance of the finger patterns that probably is correct in many respects, although it does not fully solve the problem. The cutaneous ridges make their first appearance on the finger tips at the beginning of the 4th embryonic month Towards the end of foetal life the system is fully developed, later to change only in size and distinctness The epidermal thickness is of decisive importance for the number of ridges and the pattern they form. A thin epidermis of the *finger tips* gives relatively many loops and whorls, whereas a thick (cushioned) *epidermis* gives mainly arches If broad or narrow cushioned streaks are found a mixed pattern may be



Fig. 34.—*Iris from 2 different individuals. 1) The frontal boundary layer extends rather near to the edge of the pupil; but it presents considerable diffuse atrophy with large crypts, specially inferiorly.* Various *concentric contraction furrows are seen. 2) Considerable central atrophy of the frontal boundary layer; some crypts and scratches are seen in the outer zone (after Eskelund).*

of pigment in the frontal layer of the iris, which is so dark that it is difficult to distinguish the iris from the pupil. The eye colour may, like the hair colour, grow darker with increasing age.

Finger Prints, Palmar and Plantar Patterns. The skin of fingers, toes, palms, and soles of the feet differs from the remaining skin in that it has cutaneous ridges arranged in certain patterns varying from individual to individual. The cutaneous ridges of the distal phalanges of the 10 fingers have attracted particular attention. Examinations have shown that these ridges differ so much that the pattern is never quite the same in two individuals. Each individual has a unique pattern. In no person are the patterns of like fingers on the left and the right hand identical in detail. The dactylodiagram and other dermatoglyphic traits are used for identification.

Family investigations have shown that the cutaneous patterns depend to a considerable extent on hereditary factors, but the problem has not yet been fully elucidated. In one-egg twins the cutaneous patterns are in the main concordant, but never quite identical. Mirror imaging is often seen, the finger pattern of the right hand of one twin corresponding to that of the left hand of the other.

The most important types of pattern of the finger tips are arches, loops, and whorls (*vide* Fig. 35). The loops may be ulnar or radial, i.e. open towards the ulnar or the radial side of the finger. The loop is wedged in

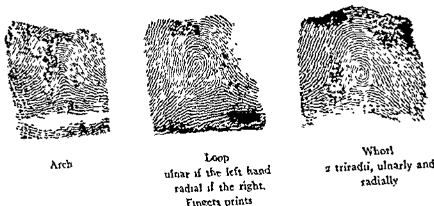


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hallucal and 3 interdigital areas The palmar main lines or creases also show variations. Twin studies have revealed that these variations are of a hereditary nature to a rather great extent

Dermatoglyphic traits give evidence of the difficulty of elucidating the inheritance of normal polymerically determined characters. In spite of comprehensive studies by special methods, which we have been able to give a quantitative character, we have by no means succeeded in clearing up the inheritance of the cutaneous ridges It is polymeric and complicated by variable penetrance and expressivity

THE OSSEOUS SYSTEM. The various bones differ considerably in size and shape from individual to individual. The bones have been extensively measured and described by anthropologists. Many of these differences are, however, paratypic, but various investigations have also been made into their heredity

The spine may present an increased number of vertebrae within a certain segment, sacralisation, cervical ribs, supernumerary thoracic vertebrae and ribs, and the like It has been impossible to find any system of inheritance of each of these abnormalities This is because hereditary factors only cause a developmental tendency in a certain direction which manifests itself by a displacement upwards or downwards of the lines of demarcation between the different segments, cervical, thoracic, lumbar, and sacral vertebrae. The upward tendency is dominant to the downward tendency One-egg twins always show the same tendency

The Shape of the Skull has always interested anthropologists and race biologists, although this may also be subject to environmental influence. That the shape is genotypically determined appears from both twin and family studies It is due to polymeric genes The cranial measure subject to the greatest interest is the cephalic index, i e the ratio between the largest breadth and the largest length of the skull expressed in percentage If the cephalic index is over 80 the individual concerned is designated as brachycephalic If under 75 as dolichocephalic, and if between 75 and 80 as mesocephalic Brachycephaly and dolichocephaly have, though with doubtful justification, been regarded as characteristic racial properties It is the most frequently measured of all anthropological indices It bears no relation to the functional anatomy of the brain and does not seem to be linked to anything else in particular.

The individual features in the skeleton of the face are likewise markedly hereditary, as are also the nasal sinuses and the mastoid air cells. The same is the case with the teeth, which, of course, are also greatly exposed to para-

formed. 2 genes at least are presumably active for the development of epidermal cushioning. The courses of nerve branches and blood vessels in the distal phalanges also play a part. To these may be added mechanical agents, such as surface curve, which again is related to the epidermal thickness The pattern is inherited mainly on the basis of 3 mutually independent gene pairs. one gene, V, *has an influence on the thickness of* the skin, a second, R, produces the radial, and a third, U, the ulnar epidermal cushioning. A varying number of ridges now occur between the triradius and the centre. The number is the greater the thinner the epidermis. Thin epidermis (22 ridges or more) is recessive (vv) to thick (6 to 15 ridges), while heterozygotes (Vv) show 16 to 21 *ridges. Cushioning, radial* as well as ulnar, is dominant to no cushioning. In addition to these main factors various modifying factors must be supposed to assert themselves, among other reasons because the 2 hands differ from each other to a greater or smaller extent. In Germany 10 to 15 per cent belong to the genotype VV, while the remaining are almost equally distributed between the types Vv and vv Nearly 50 per cent of the population are RR, against only 6 per cent rr, and nearly 50 per cent are of the type Uu, while there are 25 per cent of each of the types uu and UU

As appears from table 6 the frequencies of the pattern types differ in the different races The distribution among West Greenlanders has been compared with those of East Greenlanders and Danes It is seen that the East Greenlanders, who are of pure unmixed Eskimo race have more whorls and fewer arches and loops than the Danes, who in this respect are almost like others of white race The West Greenlanders, on the other hand, and the Eskimos in Alaska, who racially are rather mixed, are in an intermediate position

TABLE 6

The percentage of whorls, loops, and arches of finger pattern in various racial groups
(after Rife, Cummins and Fabricius-Hansen)

	Whorls	Loops	Arches
Germans	30 8	65 0	4 1
Russians	29 7	63 0	7 3
Indians (United States)	45 0	50 0	5 0
Japanese	45 0	50 0	5 0
Chinese	50 0	48 5	1 5
Negroes in Jamaica	29 0	59 2	10 8
Danes .	29 7	64 8	5 4
Dane-Eskimo hybrids (West Greenland)	42 4	54 4	3 2
Pure Eskimoes (East Greenland)	72 2	26 9	0 8

Furthermore, comprehensive investigations have been made to ascertain whether patients with certain diseases should present relatively many finger patterns of one type or the other. The result has chiefly been negative Relatively many arches and few whorls have been found in schizophrenic males, but not so in *schizophrenic females* The difference is, however, hardly so great as to be of practical significance

On palm and sole great variations are seen in the cutaneous ridges in thenar and hypothenar eminences as well as the 4 interdigital areas, or the

nose is dominant to a flat one. In a European population a concave bridge of the nose is recessive to a convex or straight one, but in crosses between White and Negro the shape of the Negro nose is dominant to that of the White. Regarding the lips the different special forms (short upper lip, thick prolabium etc.) seem to be inherited as intermediate traits, only the so-called Habsburg lip is dominant.

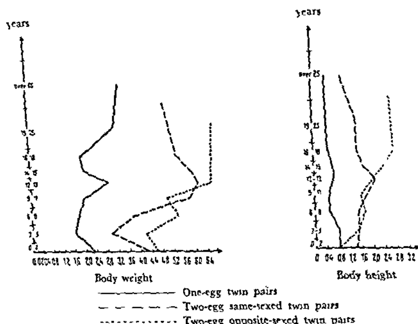


FIG 38.—Average difference between body weight and body height, expressed in per cent, in different age-classes in the two partners of twin pairs (after v. Verschuer).

The surroundings of the eyes, the eyebrows, the size, shape, and site of the eyeslits, the eyelids, the distance between the eyes mark the physiognomy and are each hereditary. In crosses between White and Mongol the Mongol fold is dominant to a normal eyelid. A similar eyelid fold occurs in Hottentots and Eskimoes, but by crossing with Whites it appears here as a recessive trait. *Epicanthus*, a sickle-shaped skin fold extending from the upper eyelid towards the lower so as to cover the medial eye corner, is probably to be regarded as a malformation of inhibition. It is seen in Mongolian idiots, among others, and is sometimes a dominant character.

The external ear presents great individual variations, in the main hereditary, as appears particularly from twin studies. This applies to the ear as a whole, its shape, length, breadth, and position, as well as to its individual

typic influence. But failing development of individual teeth, and to a certain extent the shape and position of the teeth, as well as the times of primary and secondary dentition are essentially genotypically determined.

THE FACE, ETC. A similarity of physiognomy is directly observable in relatives One-egg twins may even resemble each other so much that they are

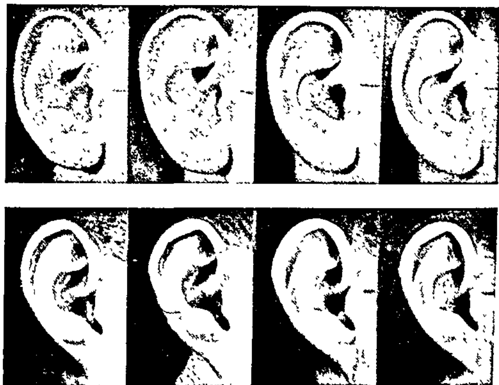


FIG. 37—Right and left ears (left mirror-reflected) from 2 one-egg twin pairs (after Quelprud)

difficult to distinguish from each other Examination of the individual features of the face will also here reveal hereditary traits, though the mode of transmission is very complicated in most cases

The development of the nose depends on a number of different genes A broad root of the nose is dominant to a narrow one in crosses of Negro and White. But within a purely White population the reverse is the case The depth of the nose, i e. the distance from the tip of the nose to the upper lip, is inherited as an intermediate trait. The tip and wings of the nose, as well as the shape and size of the nostrils are decidedly hereditary. A pointed

similarity test based mainly on anthropometric measurements. If the twins belong to different sexes and blood groups no further investigation is necessary, as they cannot possibly be identical. But if they are same-sexed and have the same blood group character, a more thorough investigation is required. Similarity on a single or a few points proves nothing, whereas similarity with regard to a great number of hereditary characters is strong evidence in favour of monozygosity. The polysymptomatic similarity test therefore consists in examining a great number of characters in the twin sibs to see whether they are alike. The result can then be compared with our experience regarding concordance of the individual characters in one-egg twins (*vide* Table 7). Our empirical knowledge within this field is, however, as yet inadequate.

At the polysymptomatic similarity test we proceed by first collecting the past *histories* of the twins with a view to birth weight, development during childhood and adolescence, previous diseases, conditions at school, and life conditions on the whole. Further, we examine whether the twins show a striking similarity in general appearance, even to the extent of being mistaken one for the other by their parents or others.

Next we proceed to the *objective examination*, which is largely anthropological. First we take notice of the *total habit*, general appearance (possibly photographs), state of nutrition, physical and mental development. Then follows examination of the *hairiness*, the hair of the head, its colour, form (possibly compared with colour scale and hair test), delimitation, possibly baldness and whorls, further, the shape and appearance of the eyebrows, *form and colour of the eyelashes*, *growth of beard*, pubic hairs, as well as presence or absence of lanugo. *The colour of the skin of face and* [illegible]

[illegible] *the forehead* and judge its inclination. We examine the *eyes and* their surroundings, the *form* and direction of the eyeslit, measure the distance of the eye angles, and describe the eyelids and position of the eyeball. A detailed description is *given of the structure* and colour of the [illegible] zones of the [illegible]
breadth and h[illegible]
nostrils, as we[illegible]
mouth and its [illegible], the heights and shapes of the upper and lower *lips*, the philtrum, and the appearance and shapes of the prolabia. The *shape* of the chin is described, and *if there is a cleft, this is noted.* We must pay attention as to whether the cheek-bones are prominent, and different facial [illegible] taken, e.g. the smallest [illegible]
of the mandibul[illegible]
hair limit. The [illegible] as its largest length and breadth may likewise be measured. We also study and describe *the teeth. The external ear* is closely *examined*, its position in relation to the head, its size, largest length and breadth, helix, anthelix, and antitragus, the sizes and shapes of the individual parts are described.

On examining *body* and *extremities* we may take a greater or smaller number of measures, e.g. stature, standing height from floor to upper sternal border, upper symphysial border, acromion, tip of 3rd finger at loose-hanging arm, ant. sup. iliac spine,

parts, such as the shape and attachment of the lobule, the development of helix, anthelix, tragus, antitragus, etc.

STATURE AND GROWTH. The stature measured for adults range from 78 to 255 cm. The extreme limits for normal stature in Denmark may probably be set at about 130 and 200 cm for males and 120 and 190 cm for females

TABLE 7.
(from Diehl and v. Verschuer)

Character	Peristatic variability in one-egg twins in %			Empirical frequency of discordance in % in two-egg twins
	Complete similarity	Similarity with small variations	Greater differences (Discordance)	
Blood groups ABO and MN[1]	100	?	0	36-38
Eye colour	86 5	13	0 5	72
Hair colour	75	22	3	77
Skin colour	87	13	0	55
Hair form	99 5	0 5	0	21
Eyebrows	98	2	0	49
Nose shape	80-85	15-20	0	65-70
Lip shape	85	15	0	ca 35
Ear shape	77	21	2	80
Cutaneous ridges (quantitatively)	81	11	8	60

[1] Complete similarity is found in one-egg twins as regards all blood groups

The average heights of the different human races range from about 140 to to about 180 cm In Denmark the average height of young men was in 1815 164 3 cm; in 1854 it had risen to 165 4 cm, in 1885 to 167.8 cm, in 1904-05 to 169 1 cm, in 1939 to 171 7 cm, and in 1949 to 173 8 cm During the past 135 years the stature has thus increased considerably, altogether 9-10 cm (*vide* p. 104).

The stature, like the growth on the whole, depends on both exogenous and endogenous factors. A certain relationship between the heights of parents and their offspring is plain to see. The stature is, however, determined by polymeric genes. Twin studies show that the growth rate or the growth rhythm likewise depends on hereditary factors There are individual differences, but the twin sibs of a one-egg pair behave essentially alike in this respect.

SIMILARITY DIAGNOSIS IN TWINS AND ANTHROPOLOGICAL PATERNITY TEST Whether twins are identical or fraternal can be settled by a polysymptomatic

similarity test based mainly on anthropometric measurements. If the twins belong to different sexes and blood groups no further investigation is necessary, as they cannot possibly be identical. But if they are same-sexed and have the same blood group character, a more thorough investigation is required. Similarity on a single or a few points proves nothing, whereas similarity with regard to a great number of hereditary characters is strong evidence in favour of monozygosity. The polysymptomatic similarity test therefore consists in examining a great number of characters in the twin sibs to see whether they are alike The result can then be compared with our experience regarding concordance of the individual characters in one-egg twins (*vide* Table 7) Our empirical knowledge within this field is, however, as yet inadequate.

At the polysymptomatic similarity test we proceed by first collecting the past *histories* of the twins with a view to birth weight, development during childhood and adolescence, previous diseases, conditions at school, and life conditions on the whole. Further, we examine whether the twins show a striking similarity in general appearance, even to the extent of being mistaken one for the other by their parents or others.

Next we proceed to the *objective examination*, which is largely anthropological. First we take notice of the *total habit*, general appearance (possibly photographs), state of nutrition, physical and *mental development*. Then follows examination of the *hairiness*, the hair of the head, its *colour*, form (possibly compared with colour scale and hair test), delimitation, possibly baldness and whorls, further, the shape and appearance of the eyebrows, form and colour of the eyelashes, growth of beard, pubic hairs, as well as presence or absence of lanugo *The colour of the skin* of face and body is examined and possibly collated with a skin colour table Notice must be taken of the presence of freckles or naevi Further, we describe *the shapes of face and head* and mention asymmetries, if present, we measure the height and breadth of *the forehead* and judge its inclination. We examine the eyes and their surroundings, the form and direction of the eyeslit, measure the distance of the eye angles, and describe the eyelids and position of the eyeball. A detailed description is given of the structure and colour of the inner and outer zones of the iris, possibly compared with an iris scale We examine [illegible]
breadth [illegible]
nos [illegible]
mo [illegible]
and [illegible]
of t [illegible] this is noted We must pay attention as to whether the cheek-bones are prominent, and different facial measures may be taken, e g the smallest frontal breadth [illegible]
of the mandibular angle, and the leng [illegible]
hair limit. The circumference of the sk [illegible]
likewise be measured We also study a [illegible]
examined [illegible]
anthelix, [illegible]

On e [illegible] may take a greater or smaller number of measures, e g stature, standing height from floor to upper sternal border, upper symphysial border, acromion, tip of 3rd finger at loose-hanging arm, ant sup iliac spine,

popliteal groove, and internal malleolus; further arm-to-arm length and sitting length, biacromial, bicristal, and bitrochanteric diameters, depth, breadth, and circumference of thorax, total arm length, lengths of upper arm, forearm, hand, and foot, and breadths of hand and foot. We must notice the shape of the spine. We examine *the cutaneous ridges* of the hand and possibly the foot, specially those of the fingers, by means of finger prints. Finally, we must remark whether abnormalities occur, such as syndactyly, warts, and others.

By comparing the results of all these examinations we can make the one-egg, or two-egg diagnosis with practically 100 per cent certainty. As a rule some of these examinations will suffice.

Paternity tests are in the main based on the same principles as the polysymptomatic similarity method If paternity can be excluded by the blood group examination alone, this will suffice If not, *an anthropological examination* on the lines indicated above is required of mother and child, as well as of the supposed father(s), to be able to pronounce on the probability of the fatherhood. The value of the anthropological examination for paternity tests is, however, limited. The children to be examined are generally young infants, and many of their properties are therefore still so slightly developed that we cannot say for certain how they will be in future life. This is, for instance, the case with eye colour and most measures of head and body A much better result can be obtained with older children, best, of course, if they are adult or nearly so But even here we cannot always draw definite conclusions, because we still know too little of the inheritance of normal traits.

Race Characters. The concept of race is difficult to define in the case of man. Race is a word that is often misunderstood Religious, linguistic, and national classifications give rise to mistakes There does not exist a race corresponding to each group of languages, country or nation Hence there has quite naturally been a tendency to replace the word race by the term "ethnic group". There is, however, no doubt about the existence of different races, though there is some disagreement as to their classification A race is defined as a group of people living within a more or less delimited area, and having certain constant normal hereditary traits in common, with not too great a range of variation. A race has been characterized as a population which differs phenotypically from all others with which it has been compared

The characters usually employed for classification of races, and therefore designated as race characters, are chiefly hereditary morphological traits, examined by anthropological measurements Instances of race characters are colour of skin, hair, and eyes, form of hair, features, shape of head, and

build of body. The race characters are assumed to possess a certain hereditary stability, because they are present in the homozygous form. Nevertheless the races change continuously and new races arise. Pure race types, where all individuals are homozygous for a relatively great number of common race characters, are comparatively rare in civilized countries, where the races are so mixed and scattered over such large areas that they are hardly recognizable.

Attempts have been made to characterize the races psychologically, but hitherto with little success, these attempts having been marked by superficiality and often also by racial prejudice

It has also been tried to classify the different races by describing their physiological peculiarities, but with no great success either, because the concept of race is so vague The blood groups cannot be regarded as race characters, they are not linked to the other race characters, but they can serve to give us information on the migration of the races in the course of time and on race mixture

Race formation takes place under influence of the various conditions of life present One of the most important factors in this connection is the climate, which has undergone marked changes during the various geological periods in which humans are known to have lived on the earth.

A certain race is produced by mutations combined with selection in the course of generations under the influence of the environment, specially the climate prevailing in a region inhabited by a fairly isolated population. Among the different human types living in the region concerned a selection occurs during the struggle for life of the types managing the best under the existing circumstances The most resistant types will survive in the long run and carry on the respective families This will gradually lead to formation of a new race type, which has adapted itself to the environment and obtained a certain constancy

The classification of humanity in races is rather arbitrary, because of the continuous mixing of races and the development of new races The concept of race is not static, but dynamic.

Coon *et al* have suggested a classification of humanity into 6 *main* races or racial stocks, viz

1 Negroid 2. Mongoloid 3 White. 4 Australoid. 5 American Indian. 6 Polynesian

In addition they have attempted a finer classification into 30 human races, but add themselves that it might have been 10 or 50

A distinction is generally made, more or less arbitrarily, between 5 main races in Europe



Northern Mediterranean Alpine

Fig 39 —European race types

1) *The Northern race* characterized as tall and slender, dolichocephalic, or at least not brachycephalic, with a long slender face, blonde hair, light (blue or grey) eyes, and a fair skin. The chin is strong-built, the nose narrow and straight or nearly straight.

2) *The Mediterranean race,* whose head and face are like those of the Northern in shape, but it has dark eyes and hair, and a brownish skin colour. The members are small or medium-sized and slender

3) *The Alpine race,* whose members are square-built, brachycephalic and have a broad face, dark eyes, brown or black hair, and a dark skin.

4) *The Dinaric race,* brachycephalic with a high head, narrow face, big convex nose, dark hair and dark eyes. It is possibly a mixture of races from Europe and Asia Minor.

5) *The East-Baltic race* is square-built, brachycephalic, with a broad mandible, a broad concave nose, light eyes, and fair hair and skin

In many parts of Europe we find, moreover, a touch of non-European races, e g from Asia Minor and North Africa

All these races are found represented in Europe and in countries peopled from Europe. In addition we find innumerable mixed types of these, as well as mixtures with other non-European races

Diseases have been studied in their relation to race It has been called *race pathology. It is well-known that the frequencies of diseases vary from* race to race, and that certain diseases are unknown in some races. Variations in the racial incidence of diseases are very often caused by environmental factors. But diseases developing on a genetic basis also differ in frequency from race to race. This is the case with erythroblastosis foetalis, as mentioned on p. 178 The incidence of Mediterranean anaemia seems particularly high in the Mediterranean countries or in people coming from these countries Sickle cell anaemia is apparently limited to Negroes Infantile amaurotic idiocy is



Dinaric East-Baltic

FIG. 40.—European race types

particularly common among Jews. Congenital dislocation of the hip is more frequent in Bavaria and the Rhenish provinces than in other parts of Germany. Many other similar instances could be mentioned.

All in all, however, most of the characteristic hereditary diseases occur *over the* whole world in all races. Komai has described the hereditary diseases and abnormalities found in the Japanese race, mentioning nearly all the hereditary diseases known in Europe and America.

Certain mental diseases as, *for instance*, manic-depressive psychosis and psychopathy were previously regarded as mainly hereditary, but some doubt seems to have arisen of late about this question. Thus, certain observations have been made to suggest that they are much rarer among primitive peoples living isolated in a pure state of nature than in the people who, irrespective of the race they belong to, live under the *mental stress of* so-called civilisation and culture, which wears them out and reduces their power of resistance. The predisposition to these diseases is hereditary, not the diseases as such.

CHAPTER 19

PHYSIOLOGICAL TRAITS

The hereditary conditions *of the* normal physiological traits have not been studied as thoroughly as those of the morphological. We know, however, a few physiological traits, in the first instance the blood groups, which show

monomeric inheritance, and which therefore afford a particularly favourable basis for genetic studies in man The blood groups will be described separately in the following chapter. The twin method has been employed to investigate the influences of environment and heredity on various physiological differences

METABOLISM, ETC. Our knowledge of the dependence of *metabolism* on hereditary factors is derived chiefly from investigations into the inheritance of metabolic diseases (*vide* p. 254). Alcaptonuria and cystinuria, where the protein metabolism is disturbed, are instances of this fact. In alcaptonuria, which generally is recessive, certain amino acids are not decomposed beyond the stage of homogentisic acid. Protein metabolism thus does not run a normal course, probably owing to absence of the enzymes regulating the final stage of the break-down of proteins. Generally speaking a dominant, normal gene conditioning the production of these enzymes must therefore exist In the case of dominant cystinuria cystine is not broken down as normally. This break-down must therefore depend on recessive normal genes. Various disturbances in carbohydrate metabolism (diabetes mellitus, glycogenosis) show that this metabolism must also depend on normal genes In hereditary lipoidosis the metabolism of the various lipoids is disturbed. In rickets, likewise dependent on hereditary factors, the calcium and phosphorus metabolism is abnormal In hereditary diabetes insipidus it is the water and salt metabolism, and in chlorosis it is the iron metabolism which differs from the normal, etc

In the cases of all these pathological metabolic processes normal genes must have been lost Correspondingly we may conclude from our knowledge of hereditary internal diseases that various normal physiological processes must be hereditary The same result has been achieved by investigations into the normal physiology of one-egg twins, of which a great number are now available, e.g. concerning basal metabolism, vital capacity, pulse rate, electrocardiogram, blood pressure, the number of blood cells, the age of the menarche, etc. One-egg twins differ less than two-egg twins with regard to these functions.

LONGEVITY AND AGEING. Another function, which is known to be normal and physiological, *the normal longevity of man*, has likewise been submitted to various genetic investigations

Several families are known in which a large proportion of the members have attained a very great age.

A Chinese family has been described, living in the neighbourhood of Canton, in which the longevity of each member is known through 19 generations 1365-1914 This

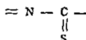
family plainly shows how the longevity of an individual depends to a great extent on those of the parents, equally on that of the mother and that of the father. An American investigation showed that the average age of children whose parents had died after the age of 80 was 52, whereas it was only 33 if both parents had died before the age of 60.

The average longevity varies considerably from one country to the other. But a comparison of the longevity of very old people, e.g. aged 90, in different countries gives a fairly constant average figure. This is because the old have a relatively uniform constitution differing from that of the bulk of the population. They are physically the fittest, a trait which is transmitted to their offspring.

Twin studies of *old twins* have shown that the physiological ageing is definitely hereditary. The hair turning gray, baldness, wrinkles, and loss of teeth occur at practically the same age and to nearly the same extent in one-egg twins. The same is the case with changes of the eye: pinguecula, arcus senilis, senile loss of the pigmented pupillary border, changes in the transparency of the lens, circumpapillary choroidal atrophy, and calcium deposits in the optic disk. The genes for various other characteristic gerontal changes in organs and tissues, such as arteriosclerosis, senile kyphosis, and the so-called senile diseases, are likewise found inherited in the fertilized egg cell, but do not manifest themselves till old age. Hereditary predisposition is an important factor in gerontology. Among twins over 60 years of age the intrapair difference in the lifespan of two-egg twins has been found to be about twice that of one-egg twin pairs.

TASTE ABILITY. In 1932 it was discovered that some people, but not all, can taste the substance phenylthiocarbamide. It has a bitter taste to those who can taste it at all. The ability to taste the substance proved to be inheritable and dominant to the lack of this ability. If we call the gene for taste ability T and the corresponding recessive gene t, then Tt and TT should be tasters and tt non-tasters. It seems, however, as if rare exceptions occur, probably due to incomplete penetrance of the taster allelomorphs. Discordance in one-egg twins with regard to the ability to taste has been observed, perhaps caused by differences in quantitative strength in the expression of the genes. The frequency of the gene t in the population can be calculated at $\sqrt{tt}$. If non-tasters constitute, say, 25 per cent of a population, t occurs at a frequency of 50 per cent. The 2 genes, T and t, are then almost equally often present. Presence or absence of taste genes does not result in completely distinct types, non-tasters being able to taste strong concentrations of phenylthiocarbamide solutions, while the ability of tasters to taste weak solutions varies somewhat. By quantitative titration of the ability to taste we find 2 distinct main groups,

tasters and non-tasters, which, however, to a certain extent overlap each oher. It has been shown that the chemical group responsible for the taste bimodality of several substances related chemically to phenylthiourea is



The taste ability and the blood group characters are still the only normal human traits known for certain to be monomeric. The hypothesis has been advanced that other normal traits should depend for their development on a single gene, e.g. mid-digital hairs, the number of circumvallate papillae, absence or presence of the peroneus tertius muscle, and the two patterns observed in phlebograms of the superficial veins of the anterior thorax recorded by infrared photography. But none of these traits have yet been proved to be monomeric.

Chapter 20

BLOOD GROUPS

The most thoroughly studied hereditary trait in man undoubtedly is that of the blood groups or the blood types.

We can determine by a rather simple examination whether an individual belongs to one blood group or another. This remains essentially unchanged throughout life, independent of environmental factors. About one hundred million people have already had their blood groups determined, and hundreds of thousands more are having their blood examined each year.

Blood grouping is of importance within many fields of medical science: to understand the haemolytic disease of the newborn, in connection with blood transfusion, to attempt to solve problems of parentage and identity, in medical genetics, anthropology, and legal medicine.

The various antigenic characters in the organism are definitely inheritable. So are also the various blood group characters, each of which presents monomeric inheritance, dependent on a single gene pair. The antigenic blood group characters are also called *receptors* Their presence was first demonstrated in the red blood cells, but some blood group antigens occur in body cells and body fluids as well. The antibodies corresponding to the antigens are found

chiefly in blood plasma or serum. They are *agglutinins* or *haemolysins*, since they agglutinate or lysate blood cells in suspension.

The amount of antibody in an antiserum can be *titrated* against a series of increasingly diluted solutions of the serum, e.g. $^1/_2$, $^1/_4$, $^1/_8$ ...; a constant quantity of known red blood cells in saline suspension is added to each dilution. The greatest dilution causing recognizable agglutination indicates the agglutinin titre of the serum. The amount of antigens or receptors of red blood cells can be measured by titrating the comparative strength of different samples of erythrocytes against the same antiserum The amount of antigens in cells or in body fluids can be titrated by measuring their ability to *absorb* or *inhibit* the corresponding antibodies The cells or the fluid are mixed with antiserum of known strength and the serum is titrated against red blood cells before and after absorption. The fall in the antibody content of the serum indicates the amount of antigen in the cells or in the fluid Agglutinins adsorbed on blood cells in suspension may be freed by *elution* from the cells by heating at 56° C. When antigen in solution is mixed with the equivalent antibody a *precipitation* may be observed.

The agglutinins found in human blood and reacting with blood cells from other humans are called *iso-agglutinins*. Similar agglutinins are found [illegible]

[illegible] animals or humans against a certain receptor by injecting a suspension of the corresponding blood cells The immunized individual will then produce antibodies against the antigen concerned These antibodies, capable of agglutinating blood cells having the *receptor*, are called *immunagglutinins* The reaction between antigen and corresponding antibody is exceedingly specific

There are found several mutually independent blood group systems. 9 have been described so far: 1) ABO blood groups and subdivisions of A. 2) MN blood groups and S subdivisions. 3) P blood groups. 4) Lewis blood groups associated with the secretor-non-secretor character. 5) Rh blood groups and several subdivisions 6) Lutheran blood groups. 7) Kell blood groups 8) Duffy blood groups. 9) Kidd blood groups.

Most of these blood group *systems are* probably inherited independently of each other; only two of them have been found to be interlinked viz. the Lutheran and the Lewis blood group systems (comp. p. 51). The genes for the other systems are then probably located on separate chromosomes, and none of them on the sex chromosomes *Further*, the gene for the ability to taste PTC (*vide* p 151), also a monomeric character, is supposed to be inherited independently of all the above blood groups If so it must be located on a separate chromosome Thus, *there* are probably "markers" in 10 of the 24 chromosomes in man and we are able to investigate whether other here-

ditary characters, including diseases, are attached to any of these 10 genes This may play a part for the mapping of the human chromosomes

THE ABO BLOOD GROUPS. The ABO blood group system was discovered by Landsteiner in 1901. On the basis of the ability of human sera to agglutinate blood cells from other humans in saline suspension we may classify all humans within the 4 blood groups: O, A, B, and AB. The antigens, the receptors A, B, and O, are present in blood cells as well as in other body cells and body fluids The antigens react with antibodies preformed in human serum, in other words, iso-antibodies, but always in the manner that an antigen and the corresponding agglutinin never occur in the same individual.

Serum from group O individuals contains antibodies, anti-A and anti-B (or α and β), which agglutinate A and B blood cells respectively and are absorbed by antigens A and B respectively Serum from A individuals contains anti-B and serum from B individuals anti-A, while AB individuals have neither anti-A nor anti-B in their serum.

The ABO blood-group characters are inheritable, dependent on 3 allelomorphs, A, B, and O. A and B both dominate completely over O, so that we cannot distinguish between groups AO and AA or BO and BB (*vide*, however, p 157), whereas A and B can be combined in one individual without the two genes noticeably affecting each other.

Afterwards it was discovered that the A group could be divided into a number of subgroups: A_1, A_2, A_3 .. The antigen A seems more strongly developed in individuals belonging to the A_1 group than in A_2 individuals. If blood cells of A_1 and A_2 are titrated against the same anti-A serum the A_1 cells show a considerably higher titre than the A_2 cells. Similarly the antigen A_3 is weaker than A_2, A_4 weaker than A_3, etc There are at least 5, possibly more, subgroups of A. Some of them differ, however, from the others not only quantitatively, but also qualitatively, since they react with slightly different antibodies A_1, A_2, and A_3 are agglutinated by all anti-A sera, A_4 and A_5 only by some of them. Nearly four-fifths of all A individuals belong to group A_1 and nearly one-fifth to group A_2 Only 0 1 per cent of all A individuals belong to A_3, while the weaker groups are extremely rare

The difference between the A groups depends on the presence of a series of multiple allelomorphs, which are also allelomorphic to B and O A_1 dominates completely over A_2, which again dominates over A_3, A_4, and A_5 All A genes dominate over the O gene

If we discount the extremely rare groups A_4 and A_5, the original 3-gene system for the ABO blood groups is extended to comprise 5 allelomorphs O, A_1, A_2, A_3, and B, which give 8 phenotypes and 15 genotypes:

TABLE 8

Phenotypes	Genotypes	Phenotypes	Genotypes
O	OO	A_3	A_3O A_3A_3
A_1	A_1O A_1A_1 A_1A_2 A_1A_3	B	BO BB
A_2	A_2O A_2A_2 A_2A_3	A_1B A_2B A_3B	A_1B A_2B A_3B

If we include A_4 the ABO system will comprise 21 genotypes and 10 phenotypes, and if also A_5 and possibly other weak A antigens, the system will be further extended

The blood group characters, as stated, remain essentially unchanged throughout life, uninfluenced by age, climate, diet, and disease The A and B agglutinins are already demonstrable early in foetal life, and are fully developed at the age of 1 or 2 years Failure of manifestation of the O, A, or B genes is never observed, and by employing a sufficiently elaborate technique we may also with great certainty distinguish between the A *subdivisions*

Blood group determinations are therefore of very great importance in connection with problems of parentage If we count in only the fairly frequent O, A_1, A_2, and B genes we may exclude paternity according to the system indicated in the Table 9

We may thus by blood group determinations disprove paternity of men belonging to certain types On the other hand, we cannot in general prove that a given man is the father If a very rare group, e g A_4 or A_5, is present in a child and the alleged *father, but* not in the mother, this fact may, however, be a certain circumstantial evidence in favour of paternity.

THE O AND H ANTIGENS Development of *the* antigens O, A, and B depends on the corresponding genes O, A, and B The anti-A agglutinin is present *in* serum from B and O individuals, and the anti-B in serum from A and O individuals These two agglutinins *have* been known ever since the discovery of the blood groups Our knowledge of the anti-O agglutinin, on the other hand, is of a more recent date, as it *occurs only* rarely in human sera and has not been demonstrated in animal sera

Ox serum contains an agglutinin capable of agglutinating O blood cells

TABLE 9

Mother	Child	Father may be	Father cannot be
O	O	O A_1. A_2. B	A_1B A_2B
,,	A_1	A_1. A_1B	O. A_2. B A_2B
,,	A_2	A_1 A_2 A_2B	O B A_1B.
,,	B	B A_1B A_2B	O. A_1. A_2
,,	A_1B	does not occur	
,,	A_2B	,, ,, ,,	
A_1	O	O A_1 A_2 B.	A_1B A_2B
,,	A_1	O. A_1. A_2 B A_1B A_2B	
,,	A_2	O A_1. A_2 B A_2B.	A_1B.
,,	B	B A_1B. A_2B	O A_1. A_2
,,	A_1B	B. A_1B. A_2B.	O A_1 A_2
,,	A_2B	B. A_1B A_2B	O. A_1 A_2.
A_2	O	O A_1 A_2 B	A_1B A_2B
,,	A_1	A_1 A_1B	O A_2 B A_2B.
,,	A_2	O A_1 A_2. B. A_2B	A_1B
,,	B	B A_1B. A_2B	O A_1 A_2
,,	A_1B	does not occur	
,,	A_2B	B A_1B. A_2B	O A_1 A_2
B	O	O. A_1 A_2 B	A_1B A_2B
,,	A_1	A_1 A_1B	O A_2 B A_2B.
,,	A_2	A_1 A_2. A_2B	O B A_1B
,,	B	O A_1 A_2. B A_1B A_2B	
,,	A_1B	A_1 A_1B	O A_2 B A_2B
,,	A_2B	A_1 A_2 A_2B	O B A_1B.
A_1B	O	does not occur	
,,	A_1	O. A_1. A_2 B. A_1B A_2B	
,,	A_2	does not occur	
,,	B	O A_1 A_2. B A_1B A_2B	
,,	A_1B	A_1 B A_1B A_2B	O A_2
,,	A_2B	A_1 A_2 A_2B	O B A_1B
A_2B	O	does not occur	
,,	A_1	A_1. A_1B	O A_2. B A_2B
,,	A_2	O A_1. A_2 B A_2B	A_1B.
,,	B	O. A_1. A_2 B. A_1B A_2B	
,,	A_1B	A_1. A_1B	O. A_2 B A_2B
,,	A_2B	A_1. A_2 B A_1B. A_2B	O

and also A blood cells, particularly A_2. Sera from other animals, e.g. goats immunized against dysentery bacilli, and eels (*Anguilla vulgaris*), as well as saliva from secretors (*vide* p. 158) likewise contain relatively large amounts of an agglutinin that can agglutinate O blood cells. However, all these apparently anti-O sera also agglutinate blood cells of other groups than O, though to a smaller extent. They are believed to react with a primary heterogenic antigen common to most blood cells, which has been named the H antigen or the H substance, and whose development is supposed to be conditioned by the H gene.

This heterogenic gene has been conceived to be an original gene from an evolutionary point of view, from which the A, B, and O genes should have developed in the course of time by a number of complete or incomplete mutations.

Where the H gene has undergone complete mutation to A or B no H remains, whereas in case of incomplete mutation a rest of the H substance persists in the blood of the individual concerned. The proportion is reciprocal, so that the sum of H and A or of H and B is always the same. The O antigen seems more closely related to H than A and B are, since the amount of H substance is generally larger in O blood cells than in A and B cells. Anti-H serum can, therefore be employed for demonstration of the O receptor, although suitable dilution is sometimes necessary. Previously it was not realized that there is a difference between the O and the H substance.

The H substance is absent only in the very few cases with complete mutation of the H gene, and these are the only cases in which the anti-O agglutinin can develop.

The proper anti-O agglutinin is therefore a rare occurrence in human serum, whereas anti-H, as already mentioned, is found in many human and animal sera. If we add saliva, from a secretor (*vide infra*), to the anti-H serum, the saliva will have an inhibitory effect on the power of the serum to agglutinate O cells, while the anti-O serum will remain uninfluenced by addition of the saliva. The O substance differs, in other words, from the H substance, and the development of the O antigen must be supposed to depend on the O gene in the same way as the A and B antigens depend for their development on the A and B genes.

Secretors and Non-Secretors. The Lewis Blood Groups. The ABO antigens are present not only in the blood *cells*, but also in various body fluids, secretions, and excretions. Absorption experiments have thus revealed O, A, and B receptors in saliva, urine, bile, spermatic fluid, liquor amnii, gastric juice, etc. Cerebrospinal fluid, sweat, and lacrimal secretion contain practi-

cally no group antigen, and in serum the antigen concentration is low. In addition, ABO antigens are found in varying amounts in most organs and tissues, except the brain. The fluid in pseudomucinous ovarian cysts contains a large quantity of ABO antigens, as much as over a hundred times of the amount present in saliva.

The remaining group antigens seem in the main to be attached to the blood At least they are present only in saliva and here only in negligible amounts. Rh and MN antigens may probably be found in some organic tissues. Amniotic fluid contains the antigen Rh when the child is Rh positive, no matter whether it is an AB secretor or not.

In 1932 it was shown that some people, secretors, secrete the ABO (or H) antigens present in their cells into the above-mentioned secretions, while others, non-secretors, do not possess this character, which is inheritable. The ability to secrete the antigens depends on a dominant gene called S. The non-secretor character depends on the recessive s. If we take, for instance, a parent combination consisting of a secretor of the AO group and a non-secretor of the BO group, the following possibilities exist for the offspring:

$$AOSs \sim BOss = \underbrace{AOSs}_{+} + AOss + \underbrace{OOSs}_{+} + OOss + \underbrace{ABSs}_{+} + ABss + \underbrace{BOSs}_{+} + BOss$$

The secretors are marked by +. The secretor and the non-secretor characters occur within all the different groups of the ABO system, being as a matter of fact completely independent thereof.

In 1946 a new antibody was discovered, which is contained in the serum of some people. The corresponding blood group was called the Lewis group, after the person in whom it was first observed Individuals whose blood cells are agglutinated by this antibody are termed Lewis positive. This character has been found to depend on at least 2 genes, which have been termed Le(a) and Le(b). Presumably there exist more allelomorphs at the Lewis locus, so we may for the present regard Le as a collective term

An individual who reacts with anti-Le(a) is characterized as Le(a+), while one who does not react with this antibody is characterized as Le(a—). Similarly we distinguish between Le(b+) and Le(b—).

In infants under 6 months of age Le(a+) behaves as a dominant character, so that the genotypes Le(a+) Le(a+) and Le(a+) Le(a—) are Lewis positive and Le(a—) Le(a—) Lewis negative From the age of 1 year and upwards Le(a—) dominates, so that only the genotype Le(a+) La(a+) is Lewis positive.

In 1948 a relationship was demonstrated between secretors and non-

secretors on one hand and the Lewis blood group on the other. The Lewis negative are secretors and the Lewis positive, with rare exceptions, non-secretors.

The frequency of non-secretors is by most writers stated to be about 20 per cent. The non-secretor character, possibly together with the Lewis group, can be of use in paternity cases, as two non-secretors cannot get a secretor child.

It has been suggested that the antigen of the secretions may be regarded as an excretion product of the blood cells. It has, however, been found to reflect a concentration of antigen in the corresponding glands. The S gene should therefore be looked upon as a complementary gene necessary for the development of the group antigen in the gland or tissue. The difference is not one of secretion or non-secretion of substances invariably present, but of production of the substances. We must distinguish between the water-soluble and the alcohol-soluble group antigens as two distinct groups of substances. The water-soluble antigens are not present in red blood cells or serum, but are present in most of the body fluids and organs of a secretor. The alcohol-soluble form of the antigen is present in tissues and in the blood cells, but not present in secretions. The water-soluble group antigens, unlike the alcohol-soluble, require a special complementary gene, the S gene, for their development.

TABLE 10

Parents	Children in %		
	M	N	MN
M∼M	100	—	—
M∼N	—	—	100
M∼MN	50	—	50
N∼N	—	100	—
N∼MN	—	50	50
MN∼MN	25	25	50

THE MN BLOOD GROUPS AND THE S SUBDIVISION. The M and N antigens of the blood cells are among the antigens against which no iso-antibodies exist. Anti-M and anti-N can be produced by injecting animals, e.g. rabbits, with M and N blood cells respectively from humans. In the serum of these animals antibodies will then develop which can agglutinate M or N cells respectively. It appears that all humans have blood cells of group M, group N, or group MN. The development of these receptors depends on two allelomorphs, neither of them dominant in respect to the other. The characters are thus inheritable, and are inherited as illustrated in Table 10.

M and N antigens develop early in the foetus and remain unchanged throughout life. The receptors are demonstrable in the blood cells, but it is not quite clear to how great an extent they are present in the remaining cells of the organism. We know of no individuals with neither M nor N, nor of any who have M in heterozygous form (MO) but not N, or N in heterozygous form (NO) but not M. There are only the three possibilities: MM, NN, and MN. In the group MN the genes slightly suppress each other.

The MN genes can be used for paternity determinations according to the following Table 11.

TABLE 11.

Mother	Child	Father can be			Father cannot be
M	M	M		MN	N
M	MN		N	MN	M
N	N		N	MN	M
N	MN	M		MN	N
MN	M	M		MN	N
MN	N		N	MN	M
MN	MN	M	N	MN	—

Recent investigations have shown that group N is divisible into two subgroups N_1 and N_2. N_1 dominates over N_2, i e N_2 is not recognizable in the genotype N_1N_2 In blood of the genotype MN_2 N_2, can easily be overlooked. N_2, however, is very rare, and we do not know exactly how the homozygous form manifests itself phenotypically The N_2 character may be regarded as a familial peculiarity, thought to be relatively common within a very limited group of people, especially so in cases of intermarriage However, this is extremely rare in the total population

The antigen N_2 is controlled by a third allelomorph N_2 at the MN locus A weak form of M and a M antigen, differing quantitatively from the ordinary M, have been described.

In 1947 a new antibody was found in human serum, which was called anti-S (it has nothing to do with the secretor gene S) It reacts with an antigen S and corresponds to a gene S, which is either allelomorphic to M and N or closely linked to these genes. There is supposed to exist a recessive gene s corresponding to the dominant gene S, but no anti-s serum has been found so far (according to a preliminary note by R A. Fisher anti-s has been identified in 1951) S and s occur exclusively in combination with M and N. S is a change which can happen both to M and N genes

There are believed to be 4 allelomorphs at the MN locus: MS, Ms, NS, and Ns. If so, we may distinguish between the phenotypes and genotypes indicated in Table 12 by means of anti-M, anti-N, and anti-S sera.

If in paternity cases we use anti-N, anti-M, and anti-S sera for blood group determinations, we may distinguish between 21 phenotypically and 55 genotypically different matings. The possibilities of exclusion of paternity will naturally thereby become considerably greater than if only anti-M and anti-N sera are used.

TABLE 12

Genotypes	Phenotypes	Genotypes	Phenotypes
MSMS	MS	MsNs	MsNs
MSMs		NSNS	NS
MsMs	Ms	NSNs	
MSNS		NsNs	Ns
MSNs	MNS		
MsNS			

The P Blood Group. The P group was discovered in 1927. Serum from a rabbit immunized with human blood cells proved to contain an antibody, anti-P, capable of agglutinating blood cells from some humans and not from others. A distinction could thus be made between P positive and P negative individuals. P is inherited as a Mendelian dominant character. The gene for P+ is termed P and that for P— p. The phenotype P then corresponds to the genotypes PP or Pp, while the phenotype p corresponds to the genotype pp. No anti-p serum has been found so far. A child cannot have the blood factor P, unless this is present in the blood of at least one of the parents.

Anti-P agglutinin occurs, though in varying, often very small quantities, in sera both from non-immunized animals and from a number of humans. It seems that if a sufficiently sensitive technique is employed anti-P can be demonstrated in serum from all P negative individuals.

There are several P allelomorphs, causing P-antigens of different strengths; all of them dominate over the gene p, and the genes causing development of a strong P antigen dominate over weak P genes. This is the reason why offspring from the mating of a P positive and a P negative parent cannot have an antigen stronger than that of the P positive parent.

The Rhesus Blood Groups. The Rh groups were discovered in 1940 by Landsteiner and Wiener. Immunization of rabbits or guinea-pigs with blood from the monkey Macacus rhesus resulted in development of antibodies ag-

M and N antigens develop early in the foetus and remain unchanged throughout life. The receptors are demonstrable in the blood cells, but it is not quite clear to how great an extent they are present in the remaining cells of the organism. We know of no individuals with neither M nor N, nor of any who have M in heterozygous form (MO) but not N, or N in heterozygous form (NO) but not M. There are only the three possibilities: MM, NN, and MN. In the group MN the genes slightly suppress each other.

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TABLE 11.

Mother	Child	Father can be			Father cannot be
M	M	M		MN	N
M	MN		N	MN	M
N	N		N	MN	M
N	MN	M		MN	N
MN	M	M		MN	N
MN	N		N	MN	M
MN	MN	M	N	MN	—

Recent investigations have shown that group N is divisible into two subgroups N_1 and N_2. N_1 dominates over N_2, i.e. N_2 is not recognizable in the genotype N_1N_2. In blood of the genotype MN_2 N_2, can easily be overlooked N_2, however, is very rare, and we do not know exactly how the homozygous form manifests itself phenotypically The N_2 character may be regarded as a familial peculiarity, thought to be relatively common within a very limited group of people, especially so in cases of intermarriage However, this is extremely rare in the total population

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In the former case the formula is

rhrh ~ RhRh = Rhrh

i.e. all the children are heterozygous Rh positives. In the latter case we arrive at the formula

rhrh ~ Rhrh = Rhrh + rhrh

i.e. half of the children are Rh positive and the other half Rh negative

If mother and child both are Rh negative, erythroblastosis will generally not occur On the whole the disease is extremely rare except when the mother is Rh negative and the child Rh positive, but cases do occur also with other combinations In a population with about 15 per cent Rh negative individuals marriages between Rh negative woman and Rh positive man will constitute about 12 per cent of all marriages, but only 1 out of 200-300 babies born is erythroblastotic. In other words, erythroblastosis must have other causes, unknown so far, in addition to the Rh incompatibility.

Normally haemolytic disease of the newborn does not develop during a woman's first pregnancy, because the Rh antibodies are not found in sufficient quantity at this time. But at the beginning of her second pregnancy the woman may have some Rh antibody, and if the second foetus likewise is Rh positive, so much antibody will be produced during this pregnancy that the child will develop erythroblastosis The same will occur in subsequent pregnancies with Rh positive foetuses In some cases the erythroblastosis does not occur till a later pregnancy than the second with a Rh positive foetus; and if there is a long interval between two pregnancies the antibodies from the former may have disappeared before the beginning of the latter. The antibody, however, often persist for decades The antibodies may also primarily originate from a blood transfusion of Rh positive blood to a Rh negative recipient. This may either cause shock at a subsequent transfusion or erythroblastosis in case of a pregnancy occurring with a Rh positive foetus, even if it is the woman's first pregnancy.

Haemolytic disease of the foetus and the newborn may be divided into the following types:

1) *Macerated foetus with hepatic cirrhosis and hydrops foetalis.* We do not know exactly how often Rhesus incompatibility is the cause of abortion, but this can hardly be a very rare phenomenon. The maceration may be of all grades The placenta is large, pale, and oedematous Maternal complications in pregnancy are common and in nearly one half of the cases the mother

glutinating the red blood cells of about 85 per cent of white people in New York.

The individuals whose red cells are agglutinated by anti-Rh are called Rh positive, while those whose red cells are not agglutinated are called Rh negative.

The gene for Rh+, Rh, is dominant to the gene for Rh—, rh. The genotypes RhRh and Rhrh are Rh+, and the genotype rhrh is Rh—.

Anti-Rh can occur in human blood, for instance 1) when a Rh negative person becomes immunized by transfusion of blood containing Rh positive blood cells, and 2) when a Rh negative woman becomes immunized while pregnant with a Rh positive foetus, which has inherited the Rh gene from its father.

In 1941 Levine, Burnham, Katzin, and Vogel showed that erythroblastosis foetalis is the result of Rh blood group incompatibility between mother and child, caused by immunization of a Rh negative mother by the Rh positive blood of her child. Anti-Rh agglutinins are produced in the blood of the mother, and the haemolytic disease of the child is caused by the subsequent passage of these maternal agglutinins through the placenta and their action *on the susceptible foetal blood*

By this discovery the cause had been found of haemolytic disease of the newborn, a severe disease, which had long been known, but the aetiology of which had hitherto been obscure At the same time we have come to know a disease which is inherited according to laws previously unknown both in general and medical genetics.

Haemolytic Disease of the Newborn Erythroblastosis foetalis was clinically recognized many years ago. Only ten years ago, however, the disease was discovered to be caused by the incompatibility of the Rh blood groups in mother and child.

*The mother is iso-immunized and the affected foetus is passively iso-*sensitized. This results in a gradual haemolytic reaction in the child Haemolysis is generally accepted as the primary mechanism of the various forms of erythroblastosis, all characterized by decay of red blood cells, extramedullary haematopoiesis, and the finding of numerous nucleated red and immature white blood cells in the peripheral blood. The disease has also been called *morbus haemolyticus neonatorum.*

The disease generally occurs in a Rh positive child born of a Rh negative woman. The mother must have the genotype rhrh and the child Rhrh, while the father's genotype can be eiter RhRh or Rhrh.

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The disease generally occurs in a Rh positive child born of a Rh negative woman. The mother must have the genotype rhrh and the child Rhrh, while the father's genotype can be eiter RhRh or Rhrh.

logical changes like those found in icterus gravis, but often less pronounced. Without treatment the mortality is relatively high, about 30 per cent, with treatment probably less than 10 per cent In cases with mild symptoms at birth, special therapy is not necessary. Indication for exchange transfusion is based on early jaundice or anaemia, a strongly positive direct Coomb's test, a high titre of Rh-antibodies in the mother's serum, or haemolytic disease in older siblings

The most efficient treatment in icterus and anaemia gravis is transfusion of Rh negative blood to the child as soon as possible after birth, preferably repeated transfusions, possibly combined with exsanguination.

Prevention of erythroblastosis has been tried in different ways. The ideal procedure would be that of determining the Rh blood group in the entire population and prevent Rh negative women from marrying Rh positive men; but the latter cannot, of course, be carried through The incidence of the disease is not higher than one in ten pregnancies providing the necessary conditions as regards Rh incompatibility are fulfilled, perhaps even still lower. Thus, the majority are protected against haemolytic disease by unknown factors Most marriages between Rh positive man and Rh negative woman will therefore not result in erythroblastotic children; and needless fear would be excited by taking too drastic preventive measures, In some places all pregnant women are submitted to Rh blood group determinations, but even this can hardly be regarded as a necessary measure

If, however, we know that an Rh positive man is married with an Rh negative woman, we may determine the anti-Rh titre in the blood at certain intervals during pregnancy An increased titre will then indicate danger of development of erythroblastosis in the *foetus* *But if* the woman has not previously born an erythroblastotic child, it is hardly an indication for induced abortion If, *on* the other hand, she has already born one or more children with erythroblastosis the operation will often be indicated, if the woman herself wants it In this connection we must also consider whether the father of the child has the genotype RhRh *or* Rhrh In the former case there is, of course, stronger indication for inducing abortion than in the latter. Generally we cannot say for certain whether the father is a homozygote or a heterozygote, but we can form a well-founded estimate of which is the more likely. We know no unfailing method of treatment to be given during the pregnancy period Premature labour is of doubtful value Injection of a strong antigen can prevent the formation of antibody, but is of no value in already immunized women The correct procedure in such cases is to let the delivery take place in hospital, where they can be ready with transfusion of Rh -- blood to the child immediately after its birth, ideally repeated transfusions with

develops hydramnios. In the foetus general oedema, anasarca, and fluid in all tissues and serous cavities are typical findings. The liver and spleen are enlarged and sometimes fibrotic. The foetus is expelled sooner or later in the pregnancy We do not know, however, how often Rh incompatibility causes early abortion. Children with universal hydrops foetalis are frequently born prematurely They are either still-born or die shortly after birth Owing to the oedema they are often markedly deformed, and in many cases they present congenital malformations, such as harelip, polydactylism, spina bifida, congenital heart defects, etc The same may be the case in the other forms of erythroblastosis The infants with hydrops are also anaemic, and often jaundiced The liver and spleen are enlarged. There is also increased haematopoiesis, haemosiderosis, erythroblastaemia, and extramedullary erythropoiesis. Hydrops foetalis is present in 10 to 20 per cent of all cases of erythroblastosis.

2) *Icterus gravis neonatorum.* Icterus gravis is the most common manifestation of haemolytic disease of the newborn. It occurs at birth or during the first few days of life. The babies are generally mature, the placenta normal, but the most characteristic sign is the intense jaundice. In addition we find enlargement of the liver and spleen, as well as a tendency to haemorrhage, and occasionally slight oedema and similar histological and haematological changes as in hydrops foetalis Death often occurs within a few days of birth. The mortality is high; the figures recorded differ somewhat, but several writers state it to be about 50 per cent, considerably smaller when treated with exchange transfusions, less than 10 per cent If the child survives, the jaundice will subside within a few weeks, but it is often succeeded by a severe anaemia, of which the child not infrequently dies at the age of 5 or 6 weeks However, the jaundice may recur.

Nuclear jaundice (kernicterus) is a frequent finding, i e a yellow staining of the grey matter of the brain, especially the basal nuclei In some cases there is also necrosis and degeneration of ganglion cells in the pigmented areas, although these changes are not generally marked

Various neurological signs, as well as mental retardation, may be seen as sequelae of haemolytic disease of the newborn, but this is uncommon There is no evidence to support the theory advanced that Rh incompatibility between mother and child is responsible for a large percentage of mental deficiency of unknown aetiology, if there has been no previous history of haemolytic disease.

3) *Anaemia gravis neonatorum* Anaemia gravis is the mildest form of erythroblastosis The anaemia may be present at birth or develop during the first week of life It is often attended by slight jaundice The liver and spleen are enlarged, and, in addition, there may occur histological and haemato-

Fisher and Race believe that the Rhesus subdivisions may be explained by assuming that there are found three pairs of antigens called

C&c, D&d, and E&e

In the following we shall principally use the nomenclature of Fisher and Race, this being the least complicated. The development of the 6 antigens depends, according to these writers, on the presence of 3 pairs of genes closely linked, Cc, Dd, and Ee. The genes in each pair are allelomorphic. Every human being possesses 2 genes from each of the 3 pairs.

The 3 genes C or c, D or d, E or e are carried close together on the same chromosome, possibly adjacent or placed within the boundary of one gene. Crossing-over of the genes has never been observed, the linkage being close or obligate. The 3 pairs of genes do not alternate, but are all present in the same individual.

A gamete from a human being can with regard to the Rh antigens be of one of the following 8 types:

cde (r), cDe (R_0), cdE (R''), cDE (R_2),
Cde (R'), CDe (R_1), CdE (R_y), CDE (R_z).

The genotype of a zygote arisen by combination of the gametes CDe and cDe, for instance, can be symbolized as

CDe/cDe or CcDDee or R_1 R_0

and the phenotype would be CDee.

Each of the 6 antigens can stimulate the production of the equivalent antibody in the blood of another organism. Anti-D (syn. anti-Rh_0) is identical with the anti-Rh first discovered.

This is the antibody produced when rabbits are immunized against Macacus rhesus blood cells, and it may also be produced by immunization of humans with no D, specially if they are of the genotype cde/cde.

The remaining 5 antibodies: anti-d, anti-C, anti-c, anti-E, and anti-e are less frequent, but they have all been found in human sera. Anti-e and anti-d were only recently discovered. The antigens corresponding to these 6 antisera have been found with the following frequencies in the English population:

C in 70 per cent	c in 80 per cent
D „ 85 „ „	d „ 65 „ „
E „ 30 „ „	e „ 96 „ „

exsanguination. Women who have given birth to one or more erythroblastotic children will as a rule be advised against another pregnancy, but sterilisation is seldom recommended. In rare cases the possibility of artificial insemination may be considered, if one does not object to this method.

It is not only Rh incompatibility which may cause haemolytic disease in the newborn. The Kell antigen K (*vide* p. 172) has in a limited number of cases been seen to cause severe erythroblastosis, also in cases where both mother and child were Rh positive. The allelomorphic antigen k has, at least in one family, brought about mild cases of haemolytic disease of the newborn

Opinion is still divided regarding the question whether the ABO antigens can provoke erythroblastosis. There seems, however, to be increasing agreement that on rare occasions they can In a heterospecific pregnancy the mother can be immunized by foetal A and B, provided the child is a secretor. Grubb *et al.* have suggested that about ten per cent of intra-uterine deaths of unknown cause can be accounted for on the ground of ABO incompatibility.

In blood transfusion it is not only injection of A blood cells into a patient with anti-A, etc. which may produce a reaction Not only the iso-agglutinins, but also the immunagglutinins may cause a transfusion reaction Many transfusion reactions are due to repeated injections of Rh positive blood into Rh negative patients. It is known that about half of the Rh negative individuals who receive Rh positive blood develop anti-Rh. The Kell antigen may also be dangerous in transfusion.

Subdivisions of the Rh Groups Soon after the discovery of the Rh group it was realized that there are several varieties of Rh antibody and also of Rh antigen. But the Rh agglutinin first discovered, the anti-Rh, now called anti-Rh_0 or anti-D, is so frequent that it is responsible for about 95 per cent of all the dangerous complications due to the Rh blood groups.

Wiener in 1941 found an anti-Rh serum which did not, like the anti-Rh first discovered, react with 85 per cent of the blood samples examined, but only with 70 per cent Other antibodies and antigens within the Rhesus groups were found soon after.

Wiener accounted for the occurrence of the new Rhesus groups on the basis of the supposed existence of 6 multiple allelic genes determining the development of 6 antigens, acting with the 6 antisera

anti-rh′ and anti-hr′
anti-Rh^0 and anti-Hr_0 and
anti-rh″ and anti-hr″

differ considerably in frequency. The 11 most frequent Rh genotypes, all with frequencies over 1 per cent, have been set out in Table 14.

Some of the 7 antisera mentioned above are, as already stated, very rare and difficult to get hold of. Many investigations into the occurrence of Rh

TABLE 14.

The most frequent Rh genotypes of English people (after Race et al. 1948).

Genetic and antigenic constitution	Short notations in common usage	Frequency in per cent
CDe/cde	R_1r	31.7
CDe/CDe	R_1R_1	16 6
cde/cde	rr	15 1
CDe/cDE	R_1R_2	11.5
cDE/cde	R_2r	11 0
CDe/cDe	R_1R_0	2 1
cDe/cde	R_0r	2 0
cDE/cDE	R_2R_2	2 0
CDe/C^wDe	$R_1R_1^w$	1 1
C^wDe/cde	$R_1^w r$	1.0
CDe/cdE	R_1R''	1 0

TABLE 15

The eight Rh groups determined by the three sera Anti-C, Anti-D and Anti-E (7317 American Whites, Unger et al 1946) Modified after Race

Phenotypes	Phenotype notation by Wiener 1949	Reaction with Anti- C	D	E	per cent
ccddee	rh	—	—	—	14 7
ccDee	Rh_0	—	+	—	2 2
ccddE	rh"	—	—	+	0 6
ccDE	Rh_2	—	+	+	15 0
Cddee	rh'	+	—	—	1 1
CDee	Rh_1	+	+	—	53 5
CddE	rh' rh"	+	—	+	0 01
CDE	Rh_1 Rh_2	+	+	+	12 9

subdivisions in the population have therefore been made with fewer sera, and information thus obtained, of course, on a smaller number of phenotypes only The 4 antisera available in many laboratories are anti-C (often also containing anti-C^W), anti-c, anti-D, and anti-E. A considerable number of Rh group investigations have been determined, as exemplified in Table 15

The Rh blood groups can be used for exclusion of paternity. If we use anti-Rh serum alone, we can only conclude that rhrh × rhrh matings cannot produce RhRh or Rhrh children By including the Rh subdivisions the pos-

Anti-C agglutinates, for instance, blood cells from individuals with one or two chromosomes which with regard to the Rh genes have one of the following formulae: CDe, Cde, CdE, or CDE. Each of these 4 chromosomes may then be combined with any other chromosomes of the 8 types found with regard to the Rh antigens.

In 1946 new genes within the Rh groups were discovered. A third gene allelomorphic to C and c, as well as an antigen called C^W, and an antibody, anti-C^W, was found. Further, a fourth and a fifth allelomorph at the C locus, called c^v and C^u, a third allelomorph at the D locus, called D^u, and a third antigen allelomorphic to E and e, called E^u. Specific antisera corresponding to the 4 last mentioned antigens have not yet been found, and they will not be considered further here.

Thus, at present 7 Rh antigens can be separated by means of specific antisera: C, c, C^W, D, d, E, and e. These 7 genes can be combined on a chromosome in twelve different ways, as indicated in Table 13. The 2 last chromosome types in the Table have not yet been observed. Fisher has calculated the frequencies of the various Rh chromosomes in the English population on the basis of blood group investigations made in England by Race *et al* (cf. Table 14) From these calculations we can, by addition, find the frequencies of the individual genes, as indicated in Table 13

The 12 chromosome types can be combined two and two in $\frac{12}{2} \times (12+1)$ or in 78 different ways. If we consider only the above 7 antigens, we must then reckon with 78 different Rh genotypes. The majority are known, but they

TABLE 13

The Frequency of Rh-chromosomes in England 1948 (modified after Race et al)

Rh gene combinations	*Short notations in common usage*	*Frequency in per cent*	*Frequency of chromosomes carrying the gene*	*per cent*
CDe	R_1	41	C	42
cde	r	39	c	57
cDE	R_2	14	C^w	1
cDe	R_0	3	D	59
C^wDe	R_1^w	1	d	41
cdE	R″	1	E	15
Cde	R′	1	e	85
CDE	R_z	0 24		
C^wde	R'^w	of very low frequency		
CdE	R_y			
C^wdE	R_z^w	not yet observed		
C^wDE	R^w			

THE INCOMPLETE OR BLOCKING ANTIBODY. The blood group antibodies first discovered act on the blood cells in saline suspension. In 1944 it appeared, however, that certain antibodies do not react with the corresponding antigens in a physiological NaCl solution During the first few years after the discovery of the Rh groups it was often stated that no anti-Rh was demonstrable in serum from Rh negative mothers of children with erythroblastosis.

This proved in many cases to be due to the fact that the antibody was incomplete, so that it did not act on the blood cells in saline solution. It is certainly fixed to them, but cannot agglutinate them in saline.

The incomplete antibodies can, however, agglutinate the blood cells, if they are suspended in serum, plasma, or another protein medium, e g. 20 per cent albumin solution instead of in saline.

The incomplete antibodies can further block the blood cells by occupying all the antigen sites on the surfaces of the cells, so that the latter cannot be agglutinated by the corresponding complete or classical agglutinins. The presence of the incomplete antibody can therefore also be demonstrated by its inhibitory effect on the activity of complete agglutinins, the so-called blocking test

The incomplete antibody, which, like other antibodies, belongs to the globulin-fraction of the serum, reacts with the erythrocytes, giving them a coat of globulin These globulin-coated cells do not agglutinate spontaneously; however, using a rabbit antibody against human globulin, the globulin-coated erythrocytes may be brought to agglutinate, and the reaction between an incomplete antibody and the corresponding erythrocyte antigen revealed. This is the so-called *Coomb's test* or the *anti-globulin test* The active principle in rabbit anti-globulin sera is anti-γ globulin

Using the anti-globulin test direct on blood cells from infants suffering from haemolytic disease it is possible to demonstrate that the blood cells have been sensitized *in utero*. In umbilical cord blood from erythroblastotic children incomplete anti-Rh has been found more frequently than complete agglutinins. The incomplete antibody probably penetrates more easily through the placenta.

The complete and incomplete antibodies are both protein in nature, mostly globulin, but are contained in different fractions of the globulin. A gradual change of one antibody function into another may be assumed. Greater differences in specificity exist between the more distinctly separated Rh groups, such as anti-C, -D, and anti-E

The effects of the antibodies (probably complex compounds of polysaccharides and amino acids) correspond to physicochemical differences in the antigens, and the reaction of antibody with antigen is reversible with a low dissociation constant. The first immunization against an antigen takes a long time, whereas restimulation of a dormant antibody occurs very quickly.

sibilities of exclusion are increased very considerably. The Rh antigens are demonstrable early in foetal life and are well-developed at birth. By using the 4 most common antisera, anti-C, anti-c, anti-D, and anti-E we can define 12 Rh groups, each reaction group usually embracing several more or less frequent genotypes. 78 matings are possible by combination of the twelve Rh groups.

If, for instance, by the 4 stated antisera, we find a mating of the following Rh groups:

ccDee ~ ccddE

the child cannot belong to any of the following Rhesus groups:

CCDE, CCddE, CCDee, CCddee,
CcDE, CcddE, CcDee, Ccddee

but may belong to one of the following:

ccDE, ccddE, ccDee, ccddee

If anti-d and anti-e sera are available as well, and the Rhesus groups of the parents are found by means of these antisera to be

ccDDee ~ ccddEE

we may conclude that the child can only belong to the Rh group ccDdEe. If it belongs to any other group we can exclude the paternity, provided there *is no doubt about the maternity.*

Once it was suspected that two children X and Y, by that time 4 years old, had been changed in the clinic where they had been born on the same day by two different mothers. The Rh blood groups of the children and their parents, found by means of anti-C, -c, -D, and anti-E sera, proved to be as follows:

the child X ccddee	the child Y CcDee
X's mother CCDee	Y's mother CcDee
X's father CcDE	Y's father CcDee

The child X is homozygous for c, and X's supposed mother homozygous for C. This is impossible, as the child must have received c from both its parents, who must therefore both have the genotype Cc or cc. The two children must thus be supposed to have been changed, as, according to the blood group, X may very well be a child of Y's supposed parents, and Y a child of X's supposed parents There was no other explanation of the state of affairs

tive bloods and 70-80 per cent of the Kell negative bloods If the new antigen is inherited as a dominant, the gene frequency in the American population will be approximately 0 52 The new system is called the *Kidd blood groups*

In addition to the 9 relatively well established blood group systems described above there are others, some of them comparatively rare, of which we have some knowledge.

The Levay antibody was found in human serum after transfusion. Anti-Gr is an iso-antibody. Both the corresponding antigens are very rare and seem to be inherited as dominant characters Anti-Jobbins is an incomplete antibody from human serum.

Further, some antibodies have been found in sera from rabbits immunized by human blood cells One of the corresponding antigens is particularly frequent among Negroes Another, called X, is present in about 95 per cent of all persons examined. An anti-q, studied particularly in Japan, is found in both animal and human sera

A few more rare or incompletely defined blood group antigens and antibodies have been mentioned in the literature; and there is reason to believe that a great many more will be discovered in future.

The so-called cold agglutinins are preformed iso-antibodies with so little affinity to the corresponding antigens that the fixation occurs only at temperatures far below body temperature

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There is, however, a considerable resemblance with regard to the blood group distribution between the North-Western European population and Whites in the U S A and Canada Among these we find about the following frequencies of the different blood group and the corresponding genes:

Frequency of group			O	45	per	cent
"	"	"	A	40	"	"
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From these figures we may calculate the gene frequencies with approximate accuracy on the basis of the following formulae, where $\overline{A}$, $\overline{B}$, and $\overline{O}$ denote the proportions of the population in the various groups.

THE LUTHERAN BLOOD GROUPS. The Lutheran antibody was discovered in blood from a patient who had been transfused many times. Lutheran was the name of the donor whose blood had stimulated the patient to produce the antibody. The antibody is an immunagglutinin called anti-Lu^a, the phenotypes Lu(a+) and Lu(a—), the genes and the antigens Lu^a and Lu^b. Lu^b can only be recognized by absence of Lu^a, because *anti-Lu^b has not yet been* found.

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The Kell antigen K is inherited as a dominant character. The recessive allelomorph is called k, and the anti-k has been identified and is known to have caused a mild form of haemolytic disease in newborn The genotypes are KK, Kk, and kk, and the phenotypes K and k or K+ and K—.

The Kell antigen is developed at birth and can be used in problems of parentage.

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An incomplete antibody, which has been called *anti-Duffy*, was recently found in the serum of a man suffering from haemophilia who had been given several blood transfusions during a period of many years

The genes of the Duffy group are called Fy^a and Fy^b, the genotypes Fy^aFy^a, Fy^aFy^b, and Fy^bFy^b, the phenotypes Fy(a+) and Fy(a—), and the antibody anti-Fy^a. Anti-Fy^b is not yet known Anti-Fy^a has caused transfusion reaction in several cases

Fy^a is dominant, and paternity is improbable if the mother and the father are Fy(a—) and the child Fy(a+), although experience is still limited with regard to this group.

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For the secretors and the Lewis groups the frequencies are: about 80 per cent secretors, and about 20 per cent Le(a+) of individuals over one year of age.

As for the Duffy group, about 65 per cent are Fy(a+).

Blood Groups and Disease As already mentioned, blood group incompatibility may cause transfusion reaction, erythroblastosis, and abortion; but otherwise there is as yet no evidence of a relationship between blood groups and disease To our knowledge the incidence and course of a disease is the same within the different blood groups. The blood group distribution also remains unchanged from one age-group to another, except for the P and Le groups, and there is no difference in longevity and vitality between persons of different blood groups The hypothesis has been advanced that maternal-foetal incompatibility should play a part in toxaemia of pregnancy, but this has not yet been confirmed

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This must be supposed to have happened long ago. Groups A and B are both demonstrable in ancient Egyptian and American mummies and skeletons, which presumably are up to about 5000 years old Further, in anthropoid apes we find blood group antigens and antibodies serologically resembling those in man In a great number of animal species there are found antigenic differences which allow a blood group classification similar to that made in the case of man Many animals even have

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For the group MN we find approximately as follows:

Frequency of group	M	28 per cent
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Frequency of the gene $M = 0.28 + \frac{0.50}{2} = 0.53$

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Regarding the gene S linked to the MN group our knowledge is as yet only limited. The frequency of this gene seems to be about 0.33.

As for the P blood groups the frequencies are somewhat lower in children than in adults, suggesting that the receptor is not fully developed at birth.

In adults the frequency of P+ = about 80 per cent

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The chance that an ovum in an Rh negative woman, which is always rh, is impregnated by a sperm cell containing Rh, with the result that the child becomes Rh positive, is thus 61 per cent

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As for the Duffy group, about 65 per cent are Fy(a+).

Blood Groups and Disease As already mentioned, blood group incompatibility may cause transfusion reaction, erythroblastosis, and abortion; but otherwise there is as yet no evidence of a relationship between blood groups and disease To our knowledge the incidence and course of a disease is the same within the different blood groups The blood group distribution also remains unchanged from one age-group to another, except for the P and Le groups, and there is no difference in longevity and vitality between persons of different blood groups The hypothesis has been advanced that maternal-foetal incompatibility should play a part in toxaemia of pregnancy, but this has not yet been confirmed.

Occurrence and Spread of the Blood Groups. It is supposed that the various blood groups have occurred by mutation in the course of time, more precisely, that the antigens on the red cells have changed now and then by mutation. Regarding the ABO group, the 3 genes are, as previously stated, believed to have arisen by mutation from a primary gene, called *H*

This must be supposed to have happened long ago Groups A and B are both demonstrable in ancient Egyptian and American mummies and skeletons, which presumably are up to about 5000 years old. Further, in anthropoid apes we find blood group antigens and antibodies serologically resembling those in man In a great number of animal species there are found antigenic differences which allow a blood group classification similar to that made in the case of man Many animals even have blood group antigens and antibodies

corresponding exactly to those occurring in man. It is therefore natural to suppose that the blood group antigens have developed repeatedly in the course of time by mutually independent, parallel mutations. Nothing is known, however, as to how often the different blood groups arise by mutation, but it is believed that some of them, e.g. the weakest A groups, may have developed fairly recently.

It seems as if the frequencies of the individual blood groups change very little with time within a given race or population, provided no great migrations or admixture of other racial elements occur. The polymorphism of the blood group antigens may be stable, kept so by a balance of selective agencies This is known as balanced polymorphism.

The blood group genes arise by mutation, but in most cases we do not *know whether they are harmful, beneficial, or neutral. It seems most natural* at present to regard the majority of the mutated genes as neutral in survival value Some of them must, however, be characterized as harmful. These must be expected to disappear again rather soon after their occurrence, in the same way as morbid genes are eliminated by natural selection If such genes are not continually replaced by mutation, we get the condition called transient polymorphism.

The Rhesus genes and other blood group genes that may cause haemolytic disease of the newborn or abortion might be expected to produce such a transient or unbalanced polymorphism.

The proportions of the two groups Rh+ and Rh— must be changing in frequency owing to the selection against the heterozygotes Hence the rarer of the two genes, *rh*, will steadily decrease in frequency, unless special conditions prevail. If a relatively large number of group Rhrh individuals die out, an equal number of Rh and rh genes are being destroyed, and the result will be the extinction of the rarer of these two genes in the population The possibility exists, however, that the rh gene is continually being replaced by mutation, though this would presuppose an unreasonably high mutation rate But other facts may also be conceived to contribute to maintaining the frequency of the Rhesus negative groups It seems as if the high frequencies of abortion and neonatal death caused by blood group incompatibility in many families are compensated for by an increased number of children. Some workers have even shown that an over-compensation often takes place, so that the lost rh genes will be replaced, and perhaps more than replaced

Blood Groups and Anthropology The relative frequencies of the various blood groups are, as stated, fairly constant within a given race or population, but differ considerably from one country to the other and in

the different races The blood group ratios may thus be designated as a racial character, but it is inherited by racial crossing independently of that which has long been understood by racial characters The blood groups have been thoroughly studied all over the world Blood group investigations have contributed rather considerably to tracing how the human races have migrated and mixed in the course of ages.

As for the ABO group distribution in Europe it has been ascertained that the frequency of O is high, that of A moderate, and of B low among Western Europeans Towards the east there is found a higher A, a moderate O, and, particularly to the east of the Baltic-Elbe-Adriatic line, among the Slavonic people, a comparatively high B frequency. B likewise becomes more common as one reaches the east and south of Asia It can actually be seen from the blood group distribution in the various countries how successive invasions from east to west has taken place in the course of time.

B is frequent among Gipsies, Hindues, Mongols, and Congo Pygmies, peoples who for a long period have been living in comparative isolation. In certain American Indians we find a O frequency of nearly 100 per cent, in others a moderate A and virtually no B, and in others again a high A and a low B. The same is seen among Eskimos and Australian Aborigines. A fairly high A frequency and some B is found in North-Western Europe, Spain, and Greece, for instance, while high A and high B occurs in Italy, Hungary, Bulgaria, Finland, Russia, and, among other places, in large parts of Asia and Africa

It has also been pointed out that A and B are concentrated in the middle of continents or in centres of population and civilisation. A and B have been thought to have a selective value over O in these regions But it is doubtful whether any one of the ABO groups has a selective value at all

It is, however, peculiar that the frequency of group O is high on the fringes of Europe, Iceland, Scotland, Ireland, North Wales, Sardinia, and in the Western Caucasus

A_1 is relatively frequent in Europe, but rare among Negroes, and totally absent in East Asia, Indonesia, Melanesia, Australia, and among the American Indians

Of the MN groups only a limited number of investigations are as yet available The frequency of M is high and that of N very low among certain American Indian and Eskimo tribes, while N is frequent among Australian Aborigines and in the people inhabiting the Islands of the Pacific. Among the New York Negroes there is a very high frequency of P positives

The distribution of the Rh groups in the different countries presents facts of considerable interest The frequency of Rh negatives is, as stated, nearly

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15 per cent in Western and Central Europe and in countries peopled from these parts of Europe; and correspondingly the frequency of the gene rh (cde) is about 40 per cent. Owing to the selection against the heterozygotes Rhrh the frequency of rh can be expected to be decreasing. Outside Europe the frequency of the rh gene is much lower. In many groups of American Indians, Indonesians, Australian Aborigines the rh frequency is zero, among Chinese and Japanese 1 or 2 per cent, and among American Negroes 7 to 8 per cent. Several of the Rh subdivisions, e.g. CDe, cDE, and cDe differ in frequency in different ethnic groups. The conditions of the Rh genes in the Basque people are of considerable interest, as shown by Mourant and others. The frequency of Rh (D) negatives among the Basques is about 29 per cent, corresponding to a rh gene frequency of about 54 per cent. There is reason to believe that the Basques are descendants of the population living in Western and Central Europe before the beginning of the immigration from east and southeast In this population there were many Rh negatives, whereas the immigrants were predominantly Rh positive. Consequently we have in this part of Europe a population in which the Rh distribution appears to be an unstable one.

Blood Groups and Problems of Parentage etc. By combined employment of all the blood group sera known it is theoretically possible to distinguish more than one million different blood group combinations and corresponding different phenotypes Many of these phenotypes are, however, so rare that they hardly ever occur But even with the antibodies now available we may in a given population distinguish between several times ten thousand different blood group combinations, all inheritable. As we know the laws according to which these characters are inherited, and as they remain unchanged throughout life, independent of environmental factors, it is evident that blood group determinations are of great value when it comes to answering the question whether a relationship between two given persons can be excluded or, possibly, must be regarded as likely

When such problems arise, blood group investigations will generally be made first, and if these give negative results, anthropological investigations will be undertaken. The latter are, however, in most cases subject to far greater uncertainty than the blood group investigations

The chances of exclusion in false accusation of paternity depend, of course, on the blood groups included in the investigation and on the frequencies of the blood groups concerned. In 1950 Race and Sanger calculated the approximate chance among Western Europeans of a man being exonerated by the blood groups of a false charge of paternity brought by a woman The

chances of exclusion on the basis of the ABO groups are nearly 17.6 per cent, of MNS 27.4 per cent, of Rh (using anti-C-c-D-E) 25.2 per cent, of Kell 4.2 per cent, of Lutheran 3.3 per cent, of secretion (or Lewis) 2.6 per cent, and of Duffy 5 per cent. By combined employment of all the stated groups the chances of exclusion amount to nearly 62 per cent.

The chances of exclusion will increase further if also the P groups are employed, as well as more Rh subdivisions, and more of the weak A groups.

The certainty with which paternity can be excluded depends on the empirical material available For the blood groups known the longest, such as ABO and MN, the empirical material is already now very large, and exclusion on account of incompatibility of these groups can take place with as great a certainty as can be obtained by any biological method. The certainty of exclusions on the basis of other blood groups is already great, and will be further increased as new empirical material is gathered.

Blood group investigations may also be useful in connection with problems of maternity, which, however, are rare. The more frequent problems of identity may arise in connection with interchanged or lost children, for instance.

Blood group investigations are a necessary aid for distinction between monozygous and dizygous like-sexed twins. Only if monozygosity cannot be excluded through blood group investigations there is reason to make a polysymptomatic identity test.

ABO blood groups can also be of aid in legal medicine, in cases requiring examination of blood stains, seminal stains, dried saliva, etc.

Chapter 21

PSYCHIC TRAITS

The hereditary transmission of the psychic faculties and peculiarities is difficult to clarify, because these are less accessible to direct observation and experimental investigations than physical traits, and because of the complex interaction of heredity and environment in mental life There can, however, be no doubt that well-defined genes *underlie* the occurrence and development of the psychic traits Genotypic differences in personality traits are obviously present and are no less important than their phenotypic plasticity.

Various fairly rough calculations of correlation have been made of the similarities of mental and physical traits in related individuals. Relatives

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Various fairly rough calculations of correlation have been made of the similarities of mental and physical traits in related individuals Relatives

seemed in the main to present the same correlation with regard to mental as to physical characters.

The question whether intelligence depends on heredity or environment has been a matter in dispute. Previously intelligence was universally believed to depend on external conditions, on education and environment. The soul of the new-born infant should then be a blank with equal potentialities for developing in a good or a bad direction, reach a high standard or be at a standstill, dependent on the conditions of life. Mentally all should from birth be equally endowed, and any difference in intellect should be due to different environmental influences. This viewpoint has, however, in the general been abandoned since we have learned to distinguish between nature and nurture. To-day heredity and environment are regarded as interacting and not as opposing concepts Nowadays nobody doubts that intelligence, like the entire mental type, is largely hereditary, and that environmental factors, including upbringing and school education, can only have a stimulating or an inhibiting effect on the hereditary factors. These determine the range within which intelligence can develop The range of variation differs from individual to individual, but seems to increase roughly proportionally to the entire mental development.

Attempts have been made by many different routes to elucidate the question of the dependence of intelligence on heredity and environment, to as great an extent as possible considering the complex nature of intelligence and the deficiency and limits of intelligence tests

Comparative studies of intellectual levels of parents and offspring, or investigations of children whose parents belong to different social classes have not given particularly obvious results, because it is so difficult to distinguish between what is due to heredity and what to environment An example of the numerous studies of this kind is given in Table 16, which is based on an investigation carried out in Württemberg village schools

Numerous investigations are also available concerning the intellectual levels of offspring and parents in cases where the children have not been brought up by their respective parents, e g. where the children are foster children or have been brought up in an infant-home It appears that children placed at a very early age in the same infant home differ mentally even though they grow up under identical external conditions, and foster and adoptive children differ in many cases very considerably from their foster parents (*vide* p 19) On the other hand, the modifying influence of home environment on intelligence-test behaviour is obvious

A person's intelligence seems in the general to be influenced but little by somatic diseases. Infection, intoxication, and mechanical lesions damaging

the cerebral tissue may, of course, produce greater or smaller intellectual defects But other diseases rarely affect intelligence directly. Deaf-mutism, blindness, and physical disablement may, indeed, inhibit the development of intelligence, but does not have an immediate influence on it. The same is probably the case with adenoid vegetations. Malnutrition of some duration

TABLE 16

Parents	Offspring in per cent		
	+	m	—
+ +	71.5	25.4	3.0
+ — / — +	33.4	42.8	23.7
mm	18.6	66.9	14.5
— —	5.4	34.4	60.1

+ indicates high, m moderate, and — weak intellect

does not either seem to impair the intelligence, but prolonged physical debility will naturally also affect the mind and reduce the power of performing intellectually determined acts.

It has also been tried in different ways to assess the influence of systematic training on intelligence. The result has been that the proper basic elements of intelligence are influenced but little by training, whereas this may somewhat change the intelligence as a whole It is particularly the concentration of will which can be influenced by training, and there is no doubt that will plays a great part for intellectually determined performances

Twins have been extensively used for studies of heredity in connection with intelligence (*vide* p 280). The chief result of these studies is that even though environmental factors have a great influence on intelligence, hereditary factors play the greatest part for its development

It has been pointed out that intelligence is not based on the intellectual endowment alone, but also on the endothymic function of personality, the individual's activity, emotional nature, and basic disposition of mind. Twin studies have now shown that the difference between the intellectual functions is nearly 2 or 3 times greater in two-egg than in one-egg twins, while the difference between the endothymic functions is 5 to 6 times greater in two-egg than in one-egg twins Genetic investigations of character and temperament have also been attempted on the basis of twin and family studies The results are not yet quite clear, but they seem to show that the basic personality traits, the total mental habitus depends very much on here-

ditary factors. At the same time there seems to be a marked educability and plasticity as regards mental traits.

A particular interest has been taken in the question of inheritance of special forms of intelligence. Many families have been described in which numerous members possess some special talent or other. It is not the genius as such which is hereditary, but the numerous mental elements of which it is composed. The fortunate combination of all these single elements determining the occurrence of the man of genius is an extremely rare phenomenon. This is the reason why men of genius are so rare, but it does not prove, of course, that the individual elements of which their high intelligence is composed cannot each be inherited separately. It has, somewhat arbitrarily, been stated that only 1 out of 4000 persons can be designated as highly intelligent. Thus rare should be the occurrence of the fortunate combination of valuable single properties determining the eminent intelligence.

A special form of intelligence is, for instance, the talent for mathematics. This form of intelligence, as well as the absence thereof, are often familial phenomena. The same applies to talents for painting, music-playing, and other arts. This has been particularly conspicuous in some families, e g the Bach family, where 76 highly musical members have been enumerated. A positive selection or an assortative mating have, however, no doubt taken place here, as an artistically gifted individual is inclined to choose a conjugal partner with the same talents. Less sharply defined forms of intelligence, e g. a pronounced faculty for political, commercial, industrial, or other similar work, are often seen as a familial trait But here, too, exogenous factors probably play a considerable part. The son will often follow in his father's footsteps.

The question of heredity in connection with normal psychic traits will not be discussed further. Numerous investigations into this problem are available, indeed, but none of them have led to unquestionable and convincing results.

CHAPTER 22

CONSTITUTION AND CONSTITUTIONAL TYPES

CONSTITUTION, PREDISPOSITION, AND DIATHESIS Constitutional pathology, which began its main development at the beginning of the 20th century, before medical genetics had properly taken form, is marked by some obscurity.

Some workers understand by *constitution* simply the sum of the hereditary factors, in other words, the same as genotype. Others define constitution as the special nature and consequent mode of reaction characterizing the individual at a given moment The genotypically determined reactions depend, of course, to a certain extent on the external conditions under which the genotype develops. By an allergic constitution we understand a special state of hypersensitivity produced by the interaction of hereditary factors and previous extrinsic influences, manifesting itself by an allergic reaction to a renewed influence from without According to this definition the constitution should be a variable condition depending on hereditary as well as acquired properties, in reality not far different from that which we designate the phenotype It changes continuously due to the fact that the various organs and their functions are constantly influenced by the environment, including age

It has also been suggested that the human constitution is the anthropology of the individual as contrasted with the anthropology of the group. "The study of constitution attempts to relate the anatomical structure of the individual to his physiology, his temperament and other psychological qualities, and, ultimately, to his range of abilities and capacities in social behaviour", as Hooton has expressed it We cannot give an exhaustive definition of the concept of constitution which can be accepted by all workers

Predisposition has been regarded as a function of the constitution Unlike hereditary predispositions, the actual predisposition depends not only on certain genes, but also on the genotype's readiness to react, in part due to previous influence

By *diathesis* we understand an already existing reaction differing from the norm, in other words, also a function of the constitution The various diatheses have constitutional types corresponding to them. As instances of diathesis we may mention the exudative-lymphatic, the asthenic, the arthritic, and the spasmophilic forms, all more or less hereditary conditions which conceptually are difficult to define Hippocrates described a *habitus apoplecticus* (short and fat) and a *habitus phthisicus* (long and thin).

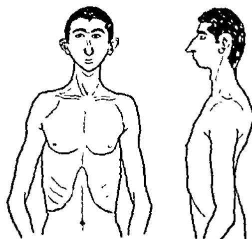


FIG. 41—Leptosomic body type.

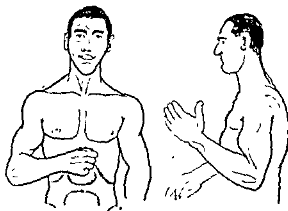


FIG 42—Athletic body type.

Instances of *pathological types of constitution* are mentioned in the section dealing with the question of heredity in endocrine diseases. These are also difficult to define. In many cases they may just as well be regarded as *formes frustes* of the corresponding diseases, and in others it is doubtful to how great an extent they can be regarded as existing in reality. Greater interest is associated with *body types* or the normal constitutional types.

BODY TYPES. Normal people plainly show different types characterized by their build of body and whole appearance. Various descriptions of these types have been given in the course of time. French clinicians, for instance, have distinguished intuitively between *type cérébral, type respiratoire, type musculaire,* and *type digestif.*

Many different classifications have been undertaken since of constitutional types. A distinction has been made between the megalosplanchnic, the normosplanchnic, and the microsplanchnic types; or between the mesoplastic (normal) and the carnivorous type; or between the hypersthenic, the sthenic, and the asthenic habitus.

Since ancient times an interest has also been taken in the question of a relationship between soul and body, whether the exterior of a person may afford a basis for conclusions about the interior. Physiognomics and phrenology are instances of this interest. The same applies to Lombroso's theory of criminal man, to the effect that a born criminal betrays his character by his appearance. He is marked by a receding forehead, coarse features, adhering ear lobes, abnormal hairiness, etc. According to Morel's well-known theory of a progressive degeneration, advanced about the middle of the 19th century, somatic signs of degeneration are also regarded as symptoms of

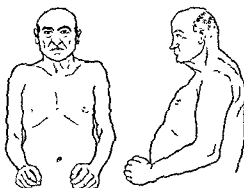


Fig 43.—Pyknic body type (after Kretschmer).

mental decadence Although there is a suggestion of truth in these old theories concerning a relationship between mental and physical traits, they were mainly speculative and rather inexact

In 1921 Kretschmer, the German psychiatrist, made a practical classification, based more on reality, into different body types. At the same time he gave convincing evidence of a certain relationship between various physical and mental properties, both in normal and in pathological conditions. His work therefore became of great importance

Kretschmer set up 3 normal body types as well as a number of pathological types, pointing out, however, that there is no sharp line of distinction between normal and abnormal types.

The 3 normal body types are the leptosomic, the pyknic, and the athletic.

The *leptosomic* (from Greek *leptos* = delicate) type is characterized by a slender and thin body The *thorax* is long and narrow, the epigastric angle acute, the neck long and thin, the shoulder breadth moderate, and the limbs moderately strongly built There is only a moderate fat deposit, and all the connective tissue is poorly developed The skull is egg-shaped with its largest diameter superiorly, the nose *prominent* in profile, forehead and chin *often* receding The mandibular angle is *very open, often* over 120°. The leptosomes often present hair anomalies, sometimes thin-hairedness without proper baldness

The leptosomes most often have a *schizothymic* psyche. They have difficulty in getting into contact with other people, being seclusive and introvert They may be faltering and shy or *firm and* fanatic Under a calm surface their minds are often torn by conflicts. To appearance they lack the power of being sympathetic with other people; but under certain circumstances they

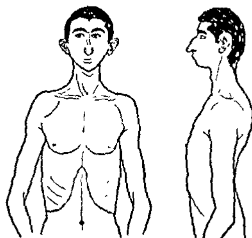


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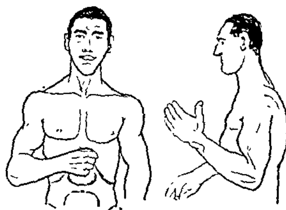


Fig. 42.—Athletic body type.

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Body Types. Normal people plainly show different types characterized by their build of body and whole appearance. Various descriptions of these types have been given in the course of time. French clinicians, for instance, have distinguished intuitively between *type cérébral, type respiratoire, type musculaire,* and *type digestif.*

Many different classifications have been undertaken since of constitutional types. A distinction has been made between the megalosplanchnic, the normosplanchnic, and the microsplanchnic types; or between the mesoplastic (normal) and the carnivorous type; or between the hypersthenic, the sthenic, and the asthenic habitus

Since ancient times an interest has also been taken in the question of a relationship between soul and body, whether the exterior of a person may afford a basis for conclusions about the interior Physiognomics and phrenology are instances of this interest. The same applies to Lombroso's theory of criminal man, to the effect that a born criminal betrays his character by his appearance. He is marked by a receding forehead, coarse features, adhering ear lobes, abnormal hairiness, etc. According to Morel's well-known theory of a progressive degeneration, advanced about the middle of the 19th century, somatic signs *of degeneration are also regarded as symptoms of*

inclined to think that still more intermediate forms exist, as one so often finds either mental or somatic features from different types combined in one person. The extreme forms of the pure types are on the verge of being pathological. The percentage distribution of the types varies from country to country, as type and race to a certain extent may be congruent

TABLE 17.

Distribution of body types among 5233 schizophrenics, 1361 manic-depressive, and 1505 epileptics (after Kretschmer).

	Body type in %				
	Pyknic	Leptosomic	Athletic	Dysplastic	Uncharacteristic
Schizophrenic	13 7	50 3	16 9	10.5	8 6
Manic-depressive	64 6	19 2	6.7	1.1	8 4
Epileptic	5 5	25 1	28 9	29 5	11.0

The relationship between body type and personality type is not absolute Most pyknics are syntonic, most leptosomes schizothymic, etc, but there are many exceptions

Kretschmer found, furthermore, a relationship between certain kinds of psychosis and body types, as indicated in Table 17 Build of body, temperament, and psychosis are co-ordinate manifestations of the same underlying constitution

In addition to the 3 normal types Kretschmer also described some *dysplastic special types*, which are more or less identical with the endocrine pathological constitutional types Dysplasia is the aspect of disharmony between regions of the *same individual* The most important dysplastic special types are those of eunuchoid stature, possibly combined with turricephaly, virilism in females, eunuchoid and polyglandular obesity, infantile or infantile-hypoplastic type of face or general infantilism, as well as acromicria with hypoplasia specifically of the hands and feet Various other pathological types of constitution have been described

A number of other investigators have on the whole confirmed Kretschmer's main findings But the procedure employed for the determination of the body type has not always been *the same* The procedure may be the rather complicated one of basing the determination on a number of head and body measurements combined with a somatoscopic estimate. A simpler method has been aimed at, with the avoidance of all estimates and determinations of the body type, relying exclusively on anthropometric measurements, possibly expressed in indices At the same time efforts have been made to reduce the number of anthropometric measurements as much as possible.

may entertain strong feelings. They often preserve an outward calm even when in a state of agitation, a calm which, however, may be interrupted by sudden unexpected outbursts of passion. We find in these people a division between feelings and behaviour, which renders them incalculable and puzzling. On the other hand, they show independence, consistency, and a faculty for abstract thinking On the whole they often have an intellectual character.

The *pyknic* (from Greek *pyknos* = compact) type is characterized by increased measures of breadth. The thorax is broad and deep, with its largest breadth inferiorly, the epigastric angle is relatively open, over 90°. Arms and legs are comparatively thin and poorly developed The skull is broad, the frontal aspect is pentagonal with parallel lateral surfaces The lateral aspect reveals a strongly built mandible. The nose is not prominent. The mandibular angle is relatively narrow, close to 90°. There is a tendency to obesity, particularly round the abdomen. The complexion is ruddy, fresh, and healthy. There is a tendency to baldness, and no abnormal hairiness is present

The pyknic body type is often associated with a *syntonic* or *cyclothymic* psyche. Pyknics feel most comfortable when harmonizing emotionally with their environments They seek contact, but are therefore also emotionally unstable. They are frank and extrovert, but their susceptibility to environmental influence often makes them rather independent and inconsistent. The pyknics are marked by common sense, readiness to help, and warm-heartedness, but on the other hand also often by shallowness, aggressiveness, and opportunism.

The *athletic* body type is characterized by a strong development of bones and muscles, broad shoulders, and relative slenderness round the hips The skull is often small with a relatively long distance between the two cheekbones, giving the impression of a broad face This type is not quite so characteristic as the two types just mentioned. Some writers (Kretschmer, among others, in some later publications) therefore hold that only 2 body types are distinguishable, the leptosomic and the pyknic

The personality associated with the athletic type is less conspicuous than in the cases of the two other types. A so-called *epileptoid* psyche, characterized particularly by a tendency to perseverance, is possibly frequent in people belonging to this body type. The epileptoid have difficulty in abandoning an idea, their feelings change but slowly, a mood persists relatively long. But at the same time they tend to be explosive with outbursts of passion, during which they may be unscrupulous and brutal, although afterwards repenting.

However, less than half of the adult population can be classified in one of these 3 types. The majority are uncharacteristic or mixed types. One is

inclined to think that still more intermediate forms exist, as one so often finds either mental or somatic features from different types combined in one person. The extreme forms of the pure types are on the verge of being pathological. The percentage distribution of the types varies from country to country, as type and race to a certain extent may be congruent.

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Wigert, for instance, has suggested an index comprising length of legs as well as thoracic breadth and circumference. Strömgren has elaborated a highly simplified anthropometric technique for determining the body type. He believes this to be determinable with sufficient accuracy, if only we know the following 3 measurements: body height, thoracic breadth, and thoracic depth Stromgren has constructed a diagram by means of which the body type can be determined on the basis of these 3 measurements.

SOMATOTYPE. No two human bodies are alike, and no two temperaments or personalities are identical Numerous attempts have been made to classify humans in different constitutional types, besides those already mentioned, and to investigate the psychological aspects of human behaviour as they are related to the morphology and physiology of the body. This may be called constitutional psychology. These attempts will not all be discussed here, but there may be reason to mention the concept of somatotype introduced by Sheldon, which includes the patterning of 3 morphological components: endomorphy, mesomorphy, and ectomorphy.

These three aspects appear also to behave in bodily morphology as if each were a separate component of structure—something which enters in different amounts into the making of a body

According to Sheldon

Endomorphy means relative predominance of soft roundness throughout the various regions of the body. When endomorphy is dominant the digestive viscera are massive and tend relatively to dominate the bodily economy

Mesomorphy means relative predominance of muscle, bone, and connective tissue. The mesomorphic physique is normally heavy, hard, and rectangular in outline Bone and muscle are prominent and the skin is made thick by a heavy underlying connective tissue.

Ectomorphy means relative predominance of linearity and fragility In proportion to his mass, the ectomorph has the greatest surface area and hence relatively the greatest sensory exposure to the outside world. Relative to his mass he also has the largest brain and central nervous system

To investigate these components Sheldon photographs the patients from three angles, front, back and side, and anthropometric measurements are made on the photographs Then it is possible to designate each subject by three numerals, one for each component The numeral 7 is assigned to the maximum manifestation, 1 to the minimum and to the amount which appears between 1 and 7 the numerals 2-6 are applied Thus 711 is an individual extreme in endomorphy and at a minimum in the other two components The 444 is the individual characterized by being at the mid-point of all three scales The measurements are compared with standard tables taking sex, age and race in consideration

In connection with the somatotype Sheldon describes three basic aspects of temperament: viscerotonia, somatotonia, and cerebrotonia

Viscerotonia is roughly identifiable with love of comfort, relaxation, sociability, conviviality, and sometimes with gluttony It is the motivational organisation dominated by the gut and by the function of anabolism. Somatotonia is the motivational pattern dominated by the will to exertion, exercise and vigorous self-expression. It is the drive toward dominance of the functions of the soma Cerebrotonia refers to the attentional and inhibitory aspect of temperament In the economy of the cerebrotonic individual the sensory and central nervous systems appear to play dominant rôles He is tense, hyperattentional and under strong inhibitory control His tendency is toward symbolic expression rather than direct action These components of temperament appear to correlate with patterns of somatotypes, and like the morphological components, they combine in various proportions in different individuals.

The value of somatotyping is, however, limited The dividing in three constitutional components is more or less artificial The body type may change during an individual's lifetime, and in many cases it is impossible to diagnose the body type in children and adolescents

Part IV

HEREDITARY DISEASES

Chapter 23

HEREDITARY DISEASES AND GENETIC PROGNOSIS

Hereditary Diseases The fact that Mendel's laws also apply to man was first demonstrated through a study of the hereditary transmission of a familial deformity. This was in 1905, when Farabee in America studied brachydactyly in 3 large families. In sibships comprising 191 individuals this abnormality occurred in 99, while 92 were normal, in other words almost a 1 to 1 ratio Other facts likewise suggested dominant inheritance.

It is characteristic that this demonstration was based on a congenital, easily observable deformity persisting unchanged throughout life and inherited *as a dominant trait dependent on a single gene*

It has since been realized that more than 500 hereditary diseases exist in man, and that not less than 2 to 3 per cent of the population suffer from *severe hereditary affections By hereditary diseases we understand those which* essentially depend on pathogenetic genes But in addition a great many are found which occur only when a hereditary predisposition is present, but which nevertheless depend, in a large measure, on environmental factors. By *endogenous* diseases we understand those which are mainly inherent in the individual himself and often depend on hereditary factors, in contradistinction to the *exogenous* diseases, which are due to extrinsic causes

In genetics we often classify living beings according to their ability to manage in the struggle for life, regarding as normal only those which can live in harmony in their surroundings From this standpoint we take it that normal people have adapted themselves to their environment Partial failure of this adaptation, possibly because the environment changes, involves disease, while total failure proves fatal.

Minor deviations from complete adaptation are called *anomalies,* but there is a gradual transition from these to proper abnormalities and diseases Biologically there is no essential difference between health and disease. Poly-

and syndactyly in their less serious forms must be regarded as anomalies. They do not affect adaptation The severer forms, on the other hand, may very well interfere with the free development of the individual by a reduced capacity for work and a diminished chance of unchecked reproduction. Defective colour vision and small stature bordering on dwarfism are also instances of anomalies. But in many cases it is difficult to say which is the norm or the normal type. The average is probably within many fields the most frequent, but we cannot therefore simply designate it as the normal or that which differs most from the pathological condition. The average man is by no means the ideal

While some diseases manifest themselves from birth, being congenital in a restricted sense, others do not give rise to signs and symptoms till later in life The hereditary diseases are often either stationary or progressive. They may, however, also show remission, or even, apparently at least, be completely cured.

Numerous hereditary diseases do not respond to treatment. They can be checked only through prevention by means of eugenic measures. Other hereditary diseases are to a great extent accessible to treatment, which, however, rarely leads to complete restoration of health. The favourable results of treatment may, on the other hand, involve a rise in the frequency of these diseases. Hence effective prevention is also important where these are concerned.

An account will be given later of the most important hereditary diseases, though not a general description of their symptomatology and treatment. Our present knowledge concerning the genetic conditions of these diseases will be reviewed their incidence in the population and whether this varies with time, place, or sections of the population; to which extent they are hereditary, elucidated particularly by twin studies; how often they arise by mutation; how pathogenetic genes manifest themselves, thereby possibly throwing light on the aetiology and pathogenesis of the diseases; whether a correlation exists between different hereditary diseases, symptoms, or syndromes; how the diseases are inherited, possibly with indication of empirical figures from propositus investigations, whether certain diseases affect the longevity and fertility of the patients; and finally, the possibilities of making a genetic prognosis and employing eugenic methods

GENETIC PROGNOSIS A common task within human genetics, of practical importance in connection with eugenic questions, is that of foretelling the hereditary characters of the contingent offspring of a certain married couple, and what probability there is that the child will suffer from one or another hereditary disease In cases where information is available on diseases in the

parents and their families such a genetic prognosis may be made in two different ways. One is called the *pure genetic prognosis* and is based on Mendel's laws, while the other is designated as the empirical genetic prognosis.

It has previously been mentioned (p. 43) how the genetic prognosis is made on the basis of Mendel's laws for monomeric dominant and recessive autosomal or sex-linked characters. But many diseases present a more complicated mode of transmission, which precludes a pure genetic prognosis.

This is, for instance, the case if the gene concerned does not show full manifestation, or if the disease is due to polymeric genes. Furthermore, we do not always know the frequencies in the population of recessive or incompletely dominant genes. We must also take into consideration the fact that hereditary diseases often arise by mutation and that we are not able to calculate exactly how often this occurs Finally, we must take account of the fact that some diseases, of whose inheritability there can be no doubt, also depend largely on external conditions. In such diseases it may be very difficult to determine the quantitative relation between exogenous and endogenous factors.

If then, for one or more of these reasons, a genetic prognosis based on Mendelian laws is out of the question, an empirical genetic prognosis is possible, provided of course the necessary empirical material is available.

To make an *empirical prognosis* means to determine the percentage chance of a given person bearing a certain familial relation to a patient inheriting the disease concerned (or possibly another disease). It is here taken for granted that these diseases, of whose genetic background we have no exact knowledge, depend essentially on hereditary factors.

Such a genetic prognosis can be made when the necessary basis for it has been procured empirically by means of a propositus investigation. We start from a number of patients with the disease to be studied and procure information on the incidence of this, and possibly also other diseases in certain groups of relatives of the propositi, e.g. parents, offspring, siblings. Empirical genetic prognosis was first used to a large extent in psychiatry, but is now also employed within other branches of medical science

Theoretically the empirical genetic prognosis has the same degree of certainty as that based on Mendelian laws, but in practice it often proves to have considerable shortcomings We cannot always depend sufficiently on the empirical material employed. Often it is not comprehensive enough and has been collected by different workers in different countries, who have used different diagnostic criteria, and made their investigations with different degrees of care and thoroughness These are, of course, drawbacks which we may hope gradually to eliminate, particularly because propositus investi-



Fig 44 a.—Acardia in twin pregnancy Owing to anastomoses connecting *from* early pregnancy the circulatory systems of the twins, the heart of the twin to the left (the acardiac one) has not developed, the consequent disturbances in the circulation of the blood have led to the monstrosity



Fig 44 b.—Deformities from constrictions by amniotic cords

gations are continually being carried out, not only to procure prognostic figures, but also for a general study of the inheritance of diseases The empirical genetic prognosis is actually no more than a preliminary aid, with which, however, we must be prepared to rest content for many years to come. But we must take care not to attach greater importance than is justified to the already existing genetico-prognostic figures

Congenital Defects and Prenatal Interactions—Congenital defects and diseases are deviations from the normal which are present at birth Such defects may be morphological or functional, they may be hereditary or acquired A non-hereditary malformation may be indistinguishable from a hereditary mutation A gene is a regulator of developmental processes which lead to the formation of a unit character. An abnormal character may depend on an abnormal gene. But a similar or identical abnormal character may appear, if the developmental processes are disturbed by environmental factors.

A continuous chain of physico-chemical reactions regulates the development of the embryo from the zygote to the complicated organism of the new-born Any interruption

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consider that the age of the mother is correlated with that of the father, the number of preceding births and the age of occurrence of the first birth.

General diseases in the mother and intra-uterine diseases in the children are intimately related. It cannot be excluded that infections in the mother or inflammatory processes in "the foetal environment" are of importance in the development of malformations, since inflammation at the site of implantation and the surface of the ovum, a failing supply of oxygen and nourishment, as well as abnormal chemical or osmotic conditions may cause disturbances in development. In experiments with mice it has been shown that when the mother lives in low oxygen tension during pregnancy many malformations may occur in the offspring

Rhesus blood group incompatibility between mother and foetus may cause malformations in the child

Injections, into pregnant mice or chick embryos, of tissue extracts or hormones may result in malformations Sex hormone injections cause abnormal development of the secondary sex characters and insulin injections give rise to a diversity of malformations

Lead, nicotine, and alcohol are generally mentioned as germ poisons and have also been supposed to cause damage to the embryo The same applies to contraceptive agents, it being uncertain, however, whether they are able to inhibit development.

Psychic trauma in the pregnant mother has time after time been designated the cause of malformations, but this has never been proved.

Chapter 24

PHYSICAL MALFORMATIONS AND DEFECTS

Serious physical malformations, especially those of a skeletal nature, occur in at least 1 per cent of all new-born infants Owing to the high mortality rate of these affections they are less frequent in the total population. The most frequent congenital hereditary physical malformations are harelip and cleft palate clubfoot, congenital dislocation of the hip, spina bifida, and anencephaly But a great number of rarer malformations exist, of which only the most important will be mentioned here Some of them are deficiencies of the skeletal system as a whole or certain parts thereof; while others are concerned with particular organs which may be defective or malformed. Genetic and environmental factors may lead to affections of the same type, to malformations of identical or similar anatomical appearance Only the hereditary deformities will be dealt with in this book

Cranial and Facial Malformations. In diseases affecting the whole osseous system, which will be described later, the head is also often deformed. In addition isolated malformations of the head are also known.

of those reactions results in damage to the embryo or foetus In general the damage is the more serious the earlier the embryo is injured.

Within the first 2-3 months of gestation, the period of organogenesis, the embryo is vulnerable, and severe malformations are easily produced. The last 6 to 7 months of gestation are essentially devoted to growth. Injuries in this period result in disease or retarded development.

Infectious, actinic, toxic, nutritional and traumatic injuries can interfere with embryonic development and cause congenital lesions.

Prenatal infection in the mother with rubella within the first 2-3 months of gestation may cause congenital cataract, heart disease, deaf-mutism or mental deficiency It has not been proved that other infectious virus diseases in the mother can cause congenital defects in the child Variola in the foetus may cause blindness and pock-marks

Prenatal infection with the protozoon toxoplasma may result in internal hydrocephalus or microcephalus, calcifications of the brain and chorioretinitis. Toxoplasmosis may begin late in foetal life just as may congenital syphilis

Exposure to larger doses of X-rays in early foetal life may lead to malformations of the extremities and the eyes, microcephaly and mental deficiency X-rays, however, probably play only a small rôle in the aetiology of human congenital lesions, while prenatal irradiation represents a means for experimental investigation into abnormal mammalian development The embryo is most sensitive to X-ray damage during 2-6 week of foetal life

In rats and pigs nutritional disturbances of the embryo have been shown to be a cause of congenital defects In the offspring of vitamin-A-deficient female animals anophthalmos, rudimentary development of the iris, coloboma of the retina, cleft palate and other deformities are observed In the offspring of female rats fed on diets deficient in riboflavin, vitamin D or minerals, many skeletal and other abnormalities have been described

Some of the congenital lesions may be sequelae of injuries in early foetal life, e g deformities due to constrictions by amniotic cords, umbilical cord slings, oligohydramnion or other space-narrowing factors such as contracted pelvis, pelvic tumours or extra-uterine pregnancy Twin pregnancies involve only a limited risk of physical deformities Anastomoses in early pregnancy connecting the circulatory systems of twins may cause malformation of the heart in one of the twins (Fig 44)

It has been supposed that an overstrained uterus, frequent births, abortions and excochleations may give rise to deformities in the foetus. The overstrained uterine mucous membrane must offer the embryo less favourable conditions than are normally present, especially so in cases of placental anomalies with reduced supply of oxygen and nourishment to the foetus. Similar conditions may, perhaps, assert themselves during the years immediately preceding the menopause

The frequency of placenta praevia of the so-called central type, which may cause malformations, increases with increasing age of mother and decreases with the number of preceding pregnancies (parity, birth rank).

An increasing proportion of deformed infants are produced by women bearing children between the maternal ages of 30 and 49 This may be due to many causes, e g. the higher mutation rate in relatively old mothers and the variable penetrance and expression of genes in the developing embryos depending on the influence of the different prenatal environments provided by young and older mothers Furthermore, we must

consider that the age of the mother is correlated with that of the father, the number of preceding births and the age of occurrence of the first birth

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Cranial and Facial Malformations In diseases affecting the whole osseous system which will be described later, the head is also often deformed. In addition isolated malformations of the head are also known

Anencephaly occurs in about 0.1 per cent of all new-born infants, more often in girls than in boys. The abnormality is sometimes seen in two or more siblings of a sibship. Hence it is likely to be hereditary, presumably recessive. In cases where a woman has born more than one anencephalic child abortion may be induced on eugenic grounds. The aetiology of anencephaly has not

TABLE 18.

The frequency of some congenital malformations.

	Incidence	
	In the population per 100 000 inhab	At birth per 100,000
Harelip (and cleft palate)	70	110
Isolated cleft palate	30	40
Club-foot (including non-congenital)	100	80
Congenital dislocation of the hip	150	100
Chondrodystrophy	*2*	*10*
Osteogenesis imperfecta congenita	—	2
Cranio-rhachischisis	—	100
Anencephaly	0	100
Absence deformities of the upper extremities	15	23
Split hands and ectrodactylism	2	3.3
Defects of radius and ulna	3	3
Amputation of upper arm	0.2	0.7
Amputation of forearm, hand or fingers	8	10
Spontaneous amputation, exogenous syndactyly	2	6
Hypospadia	150	150

yet been sufficiently elucidated. The same applies to the various types of deformed skull, *micro-, oxy-, acro-, turri-,* and *scaphocephaly,* which occasionally are seen in siblings and in some cases are hereditary *Hydrocephalus* may likewise now and then be found in siblings, and has been observed as a concordant phenomenon in one-egg twins

We know more about the hereditary transmission of *craniofacial dysostosis (Crouzon),* which is due to premature ossification of the cranial sutures, particularly the lambdoid and the coronal. It manifests itself by parrot nose and exophthalmos (frog eyes), the orbits being flattened. It is often attended by impaired vision owing to pressure atrophy of the optic nerve The malformation is concordant in one-egg twins. It may be dominant, and may probably arise by mutation, a fact which might explain its solitary occurrence in many families. Like turricephaly and acrocephalosyndactyly, craniofacial dyso-



FIG 45.—Craniofacial dysostosis (Crouzon) Mother (in the middle) with her 2 children, who have different fathers. The mother belongs to a healthy family. Hence her deformity must have arisen by mutation and then been inherited as a dominant abnormality (after Fogh-Andersen)

stosis is probably due to hyperplasia of the connective-tissue-osteoblastic system, in contrast to cleidocranial dysostosis (*vide* p 210), which is characterized by a corresponding hypoplasia

Mandibulo-facial dysostosis is due to an inhibitory process occurring at about the 7th week of embryonic life, affecting the facial bones derived from the first visceral arch The chief signs are hypoplasia of the facial bones, especially the malar bones and the mandible, and malformation of the ears. The palpebral fissures slope laterally (anti-mongoloid), and macrostomia occurs Associated anomalies, such as facial clefts, fistulae, and skeletal deformities are seen The syndrome follows an irregularly dominant mode of inheritance (Franceschetti and Klein)

Hypertelorism, likewise due to abnormal ossification of the cranial bones, and characterized particularly by great distance between the eyes, is also a dominant defect

Superior and inferior *prognathism*, the former often combined with micrognathia of the lower jaw, are dominant anomalies. Inferior prognathism is particularly frequent, being found in 1 to 2 per cent of the population

Dental anomalies are often hereditary Particularly frequent is absence of the upper lateral incisor, which is a dominant feature. An evolutionary trend to reduce human dentition in connection with shortening of the jaws has been shown to be taking place The reduction affects both ends of the rows; the third molar and the incisors, the upper lateral and the lower medial, are most likely to be missing or reduced to pegs Median diastema or trema is dominant Both environmental and hereditary factors must be taken into account in the study of malocclusion Comprehensive twin studies have shown

that dental development on the whole is highly idiotypic. The same applies to *dental caries,* which, however, also depends to a great extent on paratypic factors. *Paradentosis,* possibly combined with alveolar atrophy, is often a familial affection.

Harelip and cleft palate are very common malformations. A hereditary predisposition is the essential aetiological factor. As shown by Fogh-Andersen, there are two different malformations with no genetic connection, viz. (1) harelip with or without associated cleft palate (ha. (+ cl. pa.)) and (2) isolated cleft palate (cl. pa.). 25 per cent of the children born with harelip or cleft palate die within the first year of life, and 10 per cent of them have at birth severe associated malformations. Among the relatives of patients with harelip and cleft palate, however, no obvious increased occurrence of other affections is found to be present.

The empirical figures for the genetic prognosis in the different groups of relatives have been determined by an enumeration according to the propositus method The figures are:

for ha. (+ cl. pa.):	
Frequency among offspring of ha (+ cl. pa) patients ...	2.0 per cent
Frequency among siblings when parents are normal	4.4 "
Frequency among siblings, when one parent has ha (+ cl. pa)	14 0 "
for isolated *cl.* pa.:	
Frequency among offspring of cl. pa patients, if hereditarily tainted (otherwise probably far smaller)	7.0 "
Frequency among siblings, when parents are normal, but hereditarily tainted	12.0 "
Frequency among siblings, with no known hereditary taint	1.8 "
Frequency among siblings, when one parent has cl pa. ..	17.0 "

Most cases of ha (+ cl pa) must be supposed to be hereditary, whereas among isolated cl pa cases there is probably a considerable admixture of non-hereditary cases The most likely mode of inheritance for ha. (+ cl pa.) *is that of* "conditioned dominance" with sex limitation to males and considerably less manifestation of the heterozygous than of the homozygous form, so that in some families the affection seems dominant; but more often it appears to be of recessive nature.

Isolated cleft palate is irregularly dominant with partial sex limitation to females.

The twin material available permits no exact determination of the degree of manifestation, but it appears to be well below 50 per cent.

In the case of this affection there is generally no indication for eugenic measures, sometimes called genetic-hygienic measures (*vide* p 297). If desired by the parents, induced abortion is, however, consented to when one parent and at the same time one or more children have the malformation. A patient with harelip (and cleft palate) is generally not advised against having children;



Fig 46—Hypertelorism in grandmother and granddaughter (daughter's daughter) (after Bojlén and Brems)

but two patients with the lesion must be advised against marrying. Furthermore, such a patient must be advised against marrying a relation or a person belonging to a family in which harelip occurs If a patient with ha. (+ cl pa.) has got one child with the malformation, further offspring is advised against In case of matrimonial advice to patients with isolated cleft palate we must distinguish between solitary cases in a family and those with a hereditary taint In the latter cases pregnancy must be advised against, particularly if the patient has already got one child with the malformation. Consanguineous marriages are also advised against where isolated cleft palate is concerned. But there is no reason to prevent a patient with cl pa. from marrying one with ha. (+ cl pa), as the two affections differ genetically

Congenital torticollis, due to deficient development of the sternocleidomastoid muscle on one side, occurs as a regularly dominant defect in some

that dental development on the whole is highly idiotypic. The same applies to *dental caries,* which, however, also depends to a great extent on paratypic factors. *Paradentosis,* possibly combined with alveolar atrophy, is often a familial affection.

Harelip and cleft palate are very common malformations. A hereditary predisposition is the essential aetiological factor. As shown by Fogh-Andersen, there are two different malformations with no genetic connection, viz. (1) harelip with or without associated cleft palate (ha. (+ cl. pa.)) and (2) isolated cleft palate (cl. pa.). 25 per cent of the children born with harelip or cleft palate die within the first year of life, and 10 per cent of them have at birth severe associated malformations. Among the relatives of patients with harelip and cleft palate, however, no obvious increased occurrence of other affections is found to be present.

The empirical figures for the genetic prognosis in the different groups of relatives have been determined by an enumeration according to the propositus method. The figures are:

for ha. (+ cl. pa.):

Frequency among offspring of ha. (+ cl. pa.) patients ...	2.0 per cent
Frequency among siblings when parents are normal	4.4 „
Frequency among siblings, when one parent has ha. (+ cl. pa.)	14.0 „

for isolated cl. pa.:

Frequency among offspring of cl. pa. patients, if hereditarily tainted (otherwise probably far smaller) . ..	7.0 „
Frequency among siblings, when parents are normal, but hereditarily tainted . . .	12.0 „
Frequency among siblings, with no known hereditary taint	1.8 „
Frequency among siblings, when one parent has cl. pa. ...	17.0 „

Most cases of ha. (+ cl. pa.) must be supposed to be hereditary, whereas among isolated cl. pa. cases there is probably a considerable admixture of non-hereditary cases. The most likely mode of inheritance for ha. (+ cl. pa.) is that of "conditioned dominance" with sex limitation to males and considerably less manifestation of the heterozygous than of the homozygous form, so that in some families the affection seems dominant; but more often it appears to be of recessive nature.

Isolated cleft palate is irregularly dominant with partial sex limitation to females.

The twin material available permits no exact determination of the degree of manifestation, but it appears to be well below 50 per cent.

In the case of this affection there is generally no indication for eugenic measures, sometimes called genetic-hygienic measures (*vide* p. 297). If desired by the parents, induced abortion is, however, consented to when one parent and at the same time one or more children have the malformation. A patient with harelip (and cleft palate) is generally not advised against having children;



FIG 46.—Hypertelorism in grandmother and granddaughter (daughter's daughter) (after Bojlén and Brems).

but two patients with the lesion must be advised against marrying. Furthermore, such a patient must be advised against marrying a *relation* or a person belonging to a family in which *harelip* occurs If a patient with ha. (+ cl. pa.) has got one child with the malformation, *further offspring* is advised against. In case of matrimonial advice to patients with isolated cleft palate we must distinguish between solitary *cases in* a *family* and those with a hereditary taint In the latter cases pregnancy must be advised against, particularly if the patient has already got one child with the malformation. Consanguineous marriages are also advised against where isolated cleft palate is concerned. But there is no reason to prevent a patient with cl. pa from marrying one with ha (+ cl. pa), as the two affections differ genetically.

Congenital torticollis, due to deficient development of the sternocleidomastoid muscle on one side, occurs as a regularly dominant defect in some

families, while in others it shows irregular dominance. It is generally concordant in one-egg twins, often, however, showing a mirror image effect.

Facial asymmetry may be hereditary.

Malformations of the Vertebral Column. Significant variations are seen to occur at the site of transition from one type of vertebrae (cervical, thoracic, lumbar, sacral, and coccygeal) to the next. In one spinal column all the variations will generally be in one direction or the other. According to Kühne, hereditary variations of the vertebral column, as regards the direction of the variation, depend on one pair of allelomorphs, a dominant gene causing a tendency to cranialward variation, and a recessive gene causing a tendency to caudalward variation. These observations in combination with other anthropological characters have provided some evidence in certain paternity cases

Both kyphosis and scoliosis may occur as familial abnormalities Occasionally a very severe form of kyphoscoliosis is seen, which generally, at least without treatment, leads to humpback. It shows regularly dominant inheritance and has indicated genetic-hygienic measures. Synostosis of vertebrae may be a familial defect In Klippel-Feil's syndrome the synostoses are localized in cervical vertebrae If localized in the thoracic vertebrae they are often associated with upward dislocation of the shoulder blade, the so-called Sprengel's deformity, which is dominant in some cases, while in others it seems to be recessive.

The most frequent serious spinal deformity is *spina bifida or rhachischisis,* in some cases occurring as part of *craniorhachischisis.* Nearly 0 1 per cent of newborn infants present spina bifida aperta, but many of them die early Spina bifida often occurs as a familial deformity, most frequently in siblings. The inheritance is presumably recessive with a low manifestation rate Several genes probably cause disturbances in the development of the spinal column, but it can also be brought about by non-hereditary factors Hindse-Nielsen has investigated 124 families with at least one case of craniorhachischisis. Consanguineous marriage was found only three times among the 124 couples of parents. The greatest number of cases in one family was 7, distributed over three groups of siblings Among 12,550 persons belonging to these 124 families 50 more cases of the deformity were found In the families 131 sibships were known with at least one case each of spina bifida These 131 propositi had 548 siblings, of whom 28 (5 1 per cent) had spina bifida aperta. In these families other abnormalities are relatively frequent, such as spina bifida occulta, Klippel-Feil's syndrome, enuresis, clubfoot, hydrocephalus, other cleft formations, etc. Spina bifida is more frequent in females than in males,



Fig 47—Dominant syndactyly (after Kemp and Ravn)

and is relatively often seen in twins, in some cases it is here concordant. Spina bifida [illegible] twins. [illegible] to 20 [illegible] examined It may depend on hereditary factors, but shows considerable peristatic instability

If a woman has born *one or* more children with spina bifida aperta or craniorhachischisis the probability that her next children by the same man will have the malformation is not *very small* The morbid risk is about 5 per cent In such cases there may be an indication for genetic-hygienic measures, and it may in this connection be important to examine whether other cases of deformity occur among the relatives of one or both parents, and whether spina bifida occulta can be demonstrated radiographically in the parents.

Pectus excavatum, or funnel chest, or cobbler's breast, or koilosterna is inherited as a dominant trait, now and again skipping a generation

Congenital Dislocations. *Congenital dislocation of the hip* occurs in 1 out of 2-500 girls and in 1 out of 2-3000 boys The incidence varies considerably from one geographical locality to the other Familial accumulation is not infrequent In about one-fifth of the cases fully developed congenital dislocation of the hip is demonstrable in other members of the family. But

more often relatives present partial dislocation, or only flattening of the acetabulum, which either gives only mild symptoms or perhaps only can be demonstrated radiographically. If we take these mild forms to be manifestations of the same gene as that which produces fully developed dislocation, as we may no doubt be justified in doing, this gene shows typical dominant inheritance. But

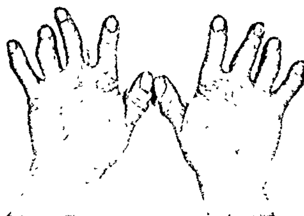


FIG. 48—Brachydactyly in a woman, aged 31, who had born 7 children, of whom 4 with brachydactyly When she got pregnant with her 8th child abortion was induced at eugenic indication.

only in about one-third of the females and in one-eighth to one-ninth of the males does the gene manifest itself as a marked diagnosable dislocation of the hip. It is, in other words, evidently a gene which is highly unstable during ontogeny. It is therefore not surprising that the various paratypic factors, such as mechanical agents in foetal life, may be of essential importance for the manifestation of the gene The reactivity of the gene may perhaps also explain the relatively favourable results of treatment by reposition and bandaging during the first few years of life

The gene being dominant, there is no reason to advise against consanguineous marriages between normal members of families with this deformity, if they have been demonstrated radiographically to have normal hip joints If one parent has the defect the offspring has 10 to 15 per cent chance of getting fully developed dislocation of the hip, and we may then be justified in complying with a request for sterilisation or induced abortion A dominant tendency to dislocation can be seen in various large joints besides the hip Often there is a general tendency to dislocations, not limited to a special joint. Dislocation of the patella may occur as a dominant trait



FIG. 49.—Ectrodactyly and cleft feet in adult female, who asks about the chance of affected offspring. Isolated case in the family

OSTEOCHONDROPATHIES. In families with congenital dislocation of the hip we also often find malum coxae senilis as well as *Calvé-Perthes' disease* or osteochondritis deformans juvenilis coxae. The latter disease is dominant in some families, while in others it occurs chiefly in siblings.

Other forms of osteochondropathy aetiologically related to Calvé-Perthes' disease are *Köhler's disease*, localized to the navicular bone of the foot and the heads of the second and third metatarsal bones, *Schlatter's disease*, concentrated chiefly in the tuberosity of the tibia, *Scheuermann's juvenile dorsal kyphosis*, and *congenital coxa vara*.

All these diseases often present familial accumulation, and they have several times been seen as concordant abnormalities in one-egg twins.

Osteochondritis dissecans is found most frequently in the elbow and knee joints. This affection is demonstrable in the distal humeral portion in 4 to 5 per cent of males, in one-quarter of the cases bilaterally. The inheritance is presumably that of irregular dominance. Concordance has been seen in one-egg twins.

EXTREMITAL MALFORMATIONS. *Poly- and syndactyly* occur in many different degrees and types. Three large completely separate families with these malformations have been described, living on the Danish island of Zealand. In some families they show typical dominance, in others irregular dominance, and in others again isolated cases are found.

Brachydactyly is also a very common dominant malformation, which may differ in site and degree. The malformation has in some very few cases been so pronounced that there has been indication for eugenic measures. In Norway Mohr and Wriedt have described a family in which two related persons, both with brachymesophalangia, married and had an only just viable child without fingers and toes and with marked deformity of the entire osseous system. If

this was not due to a mere coincidence, the gene concerned must be regarded as dominant with a recessive lethal effect. People with brachydactyly are often of small stature.

Symbrachydactyly, hypophalangia and hypoplasia of the phalanges combined with syndactyly, is practically always a unilateral deformity occurring



FIG 50—Cleft hand in a child (to the left), his mother and his mothers mother (to the right) Dominantly inherited in the family (from Birch-Jensen).

sporadically in the great majority of cases But in a few families the deformity seems to be inherited as a recessive trait.

Clubfoot (talipes varus) occurs in 0.1 per cent of new-born. It is twice as frequent in boys as in girls, and bilateral in about half of the cases. A familial predisposition is demonstrable in 15 to 18 per cent of patients with clubfoot. About 3 per cent of the siblings of these have the same deformity, but if one parent also has clubfoot the percentage rises to 8-11 Congenital clubfoot is probably hereditary in the great majority of cases Comprehensive twin studies are available on this affection They show concordance to be somewhat more frequent in one-egg than in two-egg twins The gene for clubfoot, *when present in the homozygous form, is likely to manifest itself* at a rate of 35 per cent only, more often in males than in females Bilateral clubfoot is more often concordant in one-egg twins than unilateral The conclusion has therefore been drawn that both strong and weak genes are present for this deformity. A similar deformity of the hands is occasionally seen In such families the affection shows dominance At the same time we may often find accumulation of other defects, such as kyphoscoliosis, muscular hypoplasia, spina bifida, and other physical malformations, as well as mental disturbances. Some writers hold that clubfoot always is a consequence of myelodysplasia.

In general clubfoot does not justify genetic-hygienic measures. In the rare cases with very pronounced malformation in several family members sterilisation or induced abortion may occasionally be indicated, but not so in the mild or moderately severe cases, which are by far the most frequent. As a rule there is no reason to advise patients with clubfoot against producing off-



FIG 51—Congenital amputations of both upper and lower extremities in 2 years old girl otherwise normally developed, born of normal parents in a healthy family, (after Birch-Jensen)

spring But consanguineous marriages are advised against in families with many cases of clubfoot, even if one or both partners are normal. Marriage between two patients with clubfoot is also undesirable.

Talipes valgus may also be inheritable. The same is the case with *hallux valgus, hammer toe,* and *camptodactyly,* which then show dominant inheritance

Pronounced deformities of hands and feet are rare. *Ectrodactyly* (total or partial absence of rays in hands or feet) frequently in the form of *cleft hand* or *cleft foot,* often occurs to all appearance sporadically. But in some families it shows dominant inheritance and may then justify genetic-hygienic measures

Dupuytren's contracture chiefly affects males over 40 years of age. In nearly half of the cases it is a hereditary affection, showing irregular dominance The defect being 10 times more frequent in males than in females, the latter are often unaffected carriers of the gene. In some families the affection

manifests itself at an early age. Its development is encouraged if the palm continually is exposed to minor injuries through the patient's work.

Dupuytren's contracture, like *plantar fibroma,* occurs relatively often in epileptics.

Malformations of arms and legs are rarer than malformations of hands and feet; and greater uncertainty prevails regarding their modes of transmission. They often affect only a single extremity. Genes producing defects of the proximal ends of the extremities can be regarded as sublethal factors, since foetuses with such severe defects are rarely viable.

Endogenous amputation of the upper arm occurs spontaneously in normal families There is very little chance of the deformity being inherited. Amputation of forearm and hand is always unilateral, most often left-sided The great majority of the cases are sporadic. There is, however, a slightly increased chance of other cases in the families, in which case the deformity is due either to an incompletely dominant gene or a recessive gene with low manifestation. There is no indication for eugenic measures. Similar amputations may be seen in the lower extremity. Exogenous amputations are relatively rare and differ from the endogenous by scar formations or a groove of constriction at the site of amputation. These are, of course, never inherited

Amelia (form Greek *melos* = limb) or *phocomelia* (from Greek *phoke* = seal) are both extremely rare and chiefly sporadic *Peromelia* (from Greek *peros* = crippled) is probably only rarely due to constriction by amniotic cords. Grooves of constriction are seen only in exceptional cases. As a rule the stump tapers conically. *It* is generally a recessive defect showing great variation of manifestation. That is why apparently solitary cases so often are seen in the families. The deformity also occurs occasionally in siblings, particularly in consanguineous marriages

Congenital absence of the upper or of all 4 extremities sometimes connected with highly developed micrognathia has been described as a rare (1 . 500,000) recessive malformation. The mutation has been compared with the lethal acroteriasis congenita in cattle, where recessive inheritance has been proved

Total or partial *absence of the long bones* are likewise rare defects

Total or partial radial defects and radial ray defects are regarded as due to the same gene. Radial defects are very often associated with malformations of such a nature that the patients are not viable Those who survive also have complications, among which should be mentioned congenital heart disease, which makes the prognosis considerably worse

Patients with radial defects fairly often present associated ulnar defects, hyperphalangia of the 1st digit, polydactylism of the 1st digit, spinal and thoracic deformities, as well as mental deficiency



Fig 52 —Egyptian dwarf god from about 700 A D Typical chondrodystrophic



Fig 53 —Phocomelia (Figs 52 and 53 after Trier Mørch).

Families with radial defects occasionally display accumulation of polydactylism, congenital eye and ear defects, and in rare cases aplastic anaemia.

Radial defects may be inherited as dominant, and apparently also as recessive deformities But in the great majority of the cases the deformity is not familial Very slight hypoplasia of the 1st radial ray may be inherited as a typical radial defect The inheritance is here dominant. Similarly hyperphalangia of the 1st digit may be inherited on the basis of dominant inheritance, as in the case of the defect of the radius

Practically all patients with defect of the radius have manus vara The radial defects are only very rarely attended by lesions of the lower extremities.

Dominant inheritance of the deformity is an indication for genetic-hygienic measures, there is no reason for such in sporadic cases

Apparently normal parents who have had more than one child with radial defects should be given the same advice as patients in families with dominant inheritance of the deformity.

Madelung's deformity, often dominant, is due to a disturbance of growth of the distal radial epiphysis, giving hand and forearm a characteristic bayonet shape. *Ulnar defects*, as a rule associated with ulnar ectrodactyly, may be inherited as dominant malformations; but more often they occur sporadically in the families. Patients with ulnar defects relatively often have defects of the lower extremities as well, among which fibular defects are the most common *Dislocation of the radius* may be complicated by the rare dominant *radio-ulnar synostosis*, or it may form part of a likewise dominant syndrome comprising onychatrophy, patellar defect, and dislocation of the radius. *Tibial defect* and *fibular defect* have been observed in siblings alone, but occasionally they are also seen to have been inherited directly through several generations.

GENERALIZED MALFORMATIONS. Various hereditary diseases exist which affect bones and cartilage or mesenchymal tissue in general

Chondrodystrophy occurs in almost 1 out of 10,000 new-born infants, but the great majority die within their first year of life, so the incidence in the population is only about 1 in 50,000. As shown by Trier Morch, chondrodystrophy is nearly always a dominant disease Chondrodystrophics therefore ought not to have offspring. Their power of reproduction as such is not reduced, except that the women can bear only by Caesarean section; *but their* reproductive fitness is nevertheless considerably diminished owing to the deformity, roughly to about one-fifth to one-tenth of the normal As we know that chondrodystrophy has existed since ancient times presumably with the same frequency as now, we may conclude that this deformity often arises by mutation We find 1 mutant birth (i e a chondrodystrophic born of normal parents) in 12,000, which signifies one mutant allelomorph in 24,000, or the rate of mutation per generation per gene is 1 in 24,000 or about 4×10^{-5}. Normal mothers and fathers of chondrodystrophics are older than mothers and fathers of normal children No relation can be demonstrated between season and the time of conception resulting in chondrodystrophic children They make their appearance in all classes of society, and are not born illegitimately more often than are other children No relation can be demonstrated between chondrodystrophy and diseases in parents or near relations

In animals (cattle, fowl) the gene for chondrodystrophy is dominant with a recessive lethal effect.

Anterior pituitary dwarfism has in rare cases shown recessive inheritance This deformity is, however, as a rule due to exogenous factors The so-called

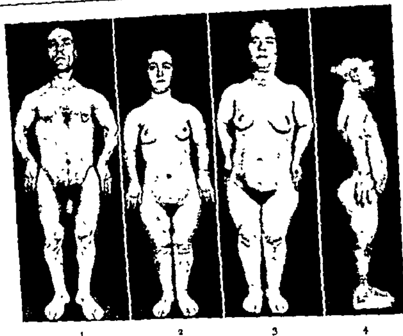


Fig 54—Chondrodystrophy. 1 and 3 are siblings Their father was a chondrodystrophic, but of a normal family Hence the disease must be supposed to have arisen by mutation 2 is daughter of 1, and 4 son of 3 (after Trier Mørch).

Hanhart's dwarfism is combined with adiposogenital dystrophy From various countries, in particular Switzerland, we know several large families, where this state is relatively frequent and shows recessive inheritance. *Primordial dwarfism* has likewise, in a very few cases, been seen to occur as a familial defect The same is the case with gigantism

Arachnodactyly (from Greek *arachne* = spider) is comparatively rare, but we do not know the exact incidence. Arachnodactyly shows the reversed symptoms of chondrodystrophy, long slender acuminated extremities with spider-like fingers and toes The build of body is asthenic, and kyphoscoliosis and funnel chest, etc are frequent associated deformities In addition these patients often present ectopia lentis (Marfan's syndrome) and congenital heart disease. The disease is dominant, but with great variation of manifestation Often some members of the family present only a few of the signs.

Osteogenesis imperfecta congenita and osteogenesis imperfecta tarda (osteopsatyrosis) are characterized by fragility of the bones, blue sclerotics, deafness due to otosclerosis, hyperlaxibility of the joints, various deformities and often dwarfism It is particularly tissue of mesenchymal origin that is

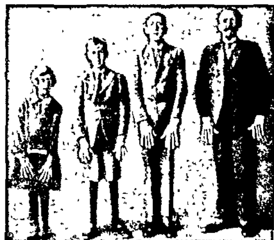
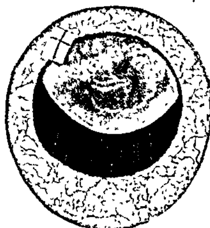



FIG 55—*Marfan's syndrome* (after Weve). Father with sons, aged 15 and 12, and daughter, aged 9, all with arachnodactyly and dislocation of the lens. To the right ectopia lentis in a boy, aged 14 (after Bücklers). In the lower portion of the pupil the distended zonular fibres are seen. The lens somewhat opaque

deficiently developed. The severe congenital and the mild forms often occur side by side in different members of the same family. Some have only blue sclerotics, while others present impaired hearing as well, and others again also bone fragility and spontaneous dislocations. This disease or its individual features show simple dominant inheritance Many solitary cases occur, however, in the families, probably due to mutation As the gene causing the disease varies considerably in its manifestation, it has been impossible to calculate its mutation rate. The eugenic measures to be taken vary for the different forms and types of the disease

Dentinogenesis imperfecta (hereditary opalescent dentine) occurs as a dominant character The structural changes of the teeth are very similar to the dental changes found in osteogenesis imperfecta

The reverse of osteopsathyrosis is *endosteal osteosclerosis* or marble bones with excessive calcification, hardening, and crispness of the compact substance, so that these patients, too, are liable to fractures The medullary cavity of the bone is diminished owing to proliferation of the osseous tissue. A distinction has been made between 3 forms of this disease: one malignant form attended with anaemia, and one without associated anaemia, and finally, a benign form The two former types are recessive, while the third is dominant.

The bone diseases mentioned so far, affect particularly the bones laid down in cartilage. But in addition we know a disease localized chiefly in the bones laid down in connective tissue This is *cleidocranial dysostosis*, a

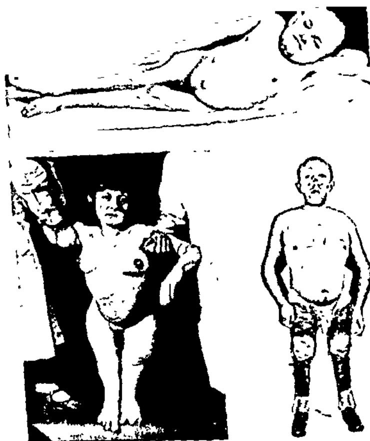


FIG 56—*Osteogenesis imperfecta* Above in a man 32 years old, isolated case in the family, severe form To the left in a woman 22 years old, isolated case in the family, rather severe case She has borne (cesarean section) a child suffering from osteogenesis imperfecta. To the right in a man 35 years old, his mother, his mother's father and his sister suffer from the same disease (medium degree).
(After Seedorff and Bierring)

comparatively rare dominant disease, characterized particularly by clavicular defects, as well as changes and defects in the cranial and facial bones, but also sometimes by rather extensive changes in the whole osseous system There is concordance in one-egg twins, and the gene nearly always manifests itself when present The few solitary cases observed must therefore presumably be due to mutation However, rare genetic types may possibly exist, which may be recessive.

In addition to these more or less generalized malformations there are found several rare, complicated syndromes, of which only a few will be mentioned: *congenital brachyrachia* or *multiple osteochondropathy*, characterized by multiple disturbances in the epiphyseal *anlage*, irregular ossification in the primary and secondary centres of ossification, and decreased growth.



FIG 57.—Cleidocranial dyostosis A mother with her two children

Osteochondrodystrophy may be divided into two forms:

1) Morquio's syndrome, which is monogenic recessive, and in which the skeletal changes are *localized largely to the vertebral column*
2) Silfverskiöld's syndrome, which is transmitted simply as a monogenic dominant character, and in which the skeletal changes are localized particularly in the extremities

Laurence-Moon-Biedl's syndrome is probably recessive. *Acrocephalosyndactyly* may be hereditary, but the mode of transmission has not yet been elucidated. A family has been observed in which a father and 2 sons presented a peculiar combination of acrocephalosyndactyly, craniofacial dysostosis, and hypertelorism. In families with these symptom complexes a single or a few of the symptoms are often seen to occur in some members of the family, while others present the whole syndrome, as mentioned p 56

Gargoylism, also called multiple dysostosis or lipochondrodystrophy (Hurler-

Pfaundler), is a congenital, often familial, probably recessive developmental disorder with multiple skeletal deformities, lipoid degeneration, enlargement of the liver and spleen, corneal opacity, and often progressive mental deficiency.

K. Bonnevie has observed a recessive abnormality in mice manifesting itself in the form of diverse malformations of head and extremities described as "myelencephalic

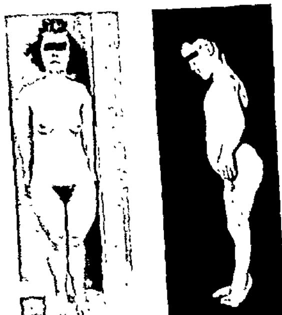


Fig 58—Osteochondrodystrophy To the right a boy 8 years old with Morquios syndrome (recessive) To the left Silfverskiölds syndrome in a woman 23 years old (dominant) (From Helweg-Larsen and Trier Morch)

blebs" These multiple defects were supposed to [illegible]

[illegible] and multiple peripheral anomalies, in short a very polyphenic syndrome

There is reason to mention another two rather commonly occurring system diseases which may lead to severe physical malformations. These are *multiple exostoses* and *multiple enchondromas* Presence of a single or a few small exostoses can hardly be regarded as a disease. But they may be so big

and extensively spread over the body that they have a deforming and disabling effect and are attended by severe complications owing to their pressure on the surrounding tissue. Both exostoses and enchondromas may be congenital, but as a rule they develop with increasing age. They are more frequent in males than in females. They show simple dominance, occasionally skipping a genera-



FIG. 59—Gargoylism, or multiple dysostosis (Hurler-Pfaundler) in two brothers 4 and 6 years old The enlargement of the liver and spleen is indicated

tion, generally through a female. Concordance of exostoses has been seen in one-egg twins; but the manifestation of the gene varies considerably Occasionally the same patients or the same families display growth disturbances, particularly of the long bones, such as general shortening, dislocation of the radius, flatfoot, etc.

Exostoses limited to the skull may also occur as a familial affection

Multiple enchondromas are rarer, but likewise hereditary

Multiple enostoses, proceeding from endosteum and growing into the medullary cavity, occasionally complicated by *disseminated lenticular dermatofibrosis,* connective tissue hyperplasia of the skin, are also dominant.

Genetic-hygienic measures have been indicated in pronounced cases of multiple exostoses, endostoses, and enchondromas.

MALFORMATIONS OF THE GENITALS We do not know the exact incidence of intersexuality, but we generally reckon that pseudohermaphrodism or hermaphrodism occurs in about 0 1 per cent of the population. According to one of the first, not particularly thorough investigations, heredity should be demonstrable in no more than about 10 per cent of the cases. The results

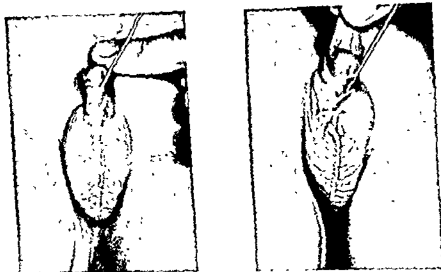


FIG 60—Hypospadia in one-egg twins (after Rahbek Sorensen).

of more recent investigations suggest, however, a higher incidence of hereditary intersexuality, though the solitary cases are in the majority.

Hermaphrodism is extremely rarely inherited direct from parents to offspring, interseves being usually sterile Patients with masculine pseudohermaphrodism occasionally marry as female partners, because their genitals have a female character Instances have been seen, however, of many years of happy married life of a masculine hermaphrodite and a normal woman; but generally no children are born in such marriages In rare cases the testes of an intersex can produce sperm cells, and it is stated that a pseudohermaphrodite living unrecognized as woman has caused a normal woman to become pregnant

In the familial instances known so far, intersexuality is inherited through unaffected females, who often have intersexes among their siblings Intersexuality occasionally occurs in 2 or more siblings. Discordance with regard to intersexuality has been seen in one-egg twins The parents of intersexes are often related.

In man and mammals all intersexes are supposed originally to have belonged to the female sex and afterwards, at some time or other during ontogeny, to have switched over in the male direction (*vide* p 88). In goat and hog hereditary female intersexuality is not infrequent.

According to Goldschmidt the sex determination depends on the balance between the male and the female sex-determining factors. On the basis of this theory intersexuality must be supposed to occur in the manner that in a female individual weak female-determining factors from the mother are brought together with strong male-determining factors from the father. The result is female intersexuality. This theory has, however, not yet been finally established.

Hypospadias, which is rather frequent, is, as stated, inherited as an irregularly dominant trait. About 75 per cent of the cases occur sporadically, however. *Epispadias* is much rarer than hypospadias Both have often shown concordance in one-egg twins

Phimosis as well as *hypoplasia of the prepuce* may be dominant.

Cryptorchism sometimes occurs in siblings. In dog and hog it has been seen as a dominant defect In man it is often discordant in one-egg twins.

Inguinal hernia, which is stated to occur in 1 out of 20 to 30 males, much less frequently in females, is concordant in just over half of one-egg twins When inherited it shows irregular dominance with a much higher manifestation rate in males than in females. In some families there is only a general predisposition to hernia (inguinal, femoral, umbilical, etc), while in others it is a certain form of hernia that is inherited.

Gynaecomastia is not infrequently a familial phenomenon. The same is the case with hyperthelia and polymastia

Chapter 25

EAR, NOSE, AND THROAT DISEASES

The incidence of deaf-mutism (congenital and early deafness) varies with time and place. It ranges from 0 04 to 0 08 per cent and is slightly higher in males than in females. The statements concerning the proportion of hereditary cases differ considerably, ranging from 10 to 80 per cent In 1940 Lindenov determined the causes of deaf-mutism in a part of the Danish population, as indicated in Table 19.

TABLE 19

The causes of deaf-mutism in 345 cases (176 males and 169 females)

	Per cent	Per cent
Hereditary deaf-mutism		45
sporadic recessive deaf-mutism . .	43	
hereditary labyrinthine deaf-mutism	2	
Acquired deaf-mutism caused by .		55
epidemic meningitis .	15	
scarlatina	6	
other infectious diseases (pneumonia, abdominal typhoid, diphtheria, morbilli, pertussis, parotitis, influenza, poliomyelitis etc)	18	
suppurative otitis media . .	6	
cong syphilis	2	
head injury .	4	
other causes .	4	

It is obvious from the figures in Table 19 that the number of cases of deaf-mutism caused by exogenous factors in all probability will decrease during coming years To-day *it is possible* to treat scarlatina, meningitis and other infectious diseases effectively, in contrast to what was the case only a decade or so ago, and head injury, intracranial haemorrhages in new-born, and other environmental factors *are much* rarer than previously Hence the proportional frequency of endogenous deaf-mutism, the percentage of hereditary cases among the total number of deaf-mutes, must be expected to increase considerably, if prophylactic measures are not taken, which have as yet been done only to a very limited extent.

The same holds true with regard to other defects and diseases, as for

instance blindness and oligophrenia. The exogenous cases are decreasing, the endogenous remain constant or are even increasing as a result of the progress of civilization. Furthermore the chances that many patients who suffer from hereditary lesions will live and propagate are becoming greater year by year, and negative genetic-hygienic measures are taken only in few countries and even in these countries generally in a rather haphazard way.

SPORADIC RECESSIVE DEAF-MUTISM. The most frequent form of hereditary deaf-mutism is the *sporadic recessive* form, the anatomical basis of which is aplasia or hypoplasia of the internal ear, the nerve trunk, and the central nuclei and tracts, i.e. a failing or deficient development of the entire nervous system of the organ of hearing. The underlying process is believed to depend *on an inhibition arising in the 5th embryonic month* Occasionally there are found remnants of hearing, which, in contrast to what is the case in acquired deaf-mutism, usually are symmetrical.

Sporadic recessive deaf-mutism is often mentioned as a paradigm of a recessive hereditary disease As might be expected, it occurs particularly in cases of intermarriage.

In 1890 9 per cent of all deaf-mutes and 23 per cent of all congenitally deaf in Denmark were born of related parents. 50 years later, in 1940, consanguinity of the parents was found in 6 per cent of all deaf-mutes, in more than 10 per cent of the hereditary cases, and in 2 per cent of the acquired Recessive deaf-mutism must therefore be expected to decrease in frequency gradually as intermarriage becomes rarer

The importance of consanguinity also manifests itself by the fact that there are comparatively *many deaf-mutes in certain remote districts*, e g, 0 145 per cent in the Vasterbotten county in Sweden as compared with 0 049 per cent in the city of Stockholm In all Sweden there are 0 093 per cent and 0 074 per cent deaf-mutes in rural and urban districts respectively

In Denmark, on the other hand, where really remote localities can hardly be said to exist, the following figures for deaf-mutes are found · In the Capital and the provincial towns 0.053 per cent and in rural district 0 026 per cent In this country there are thus twice as many deaf-mutes in the towns and cities as in the rural districts. As it can hardly be a question of greater frequency of intermarriage in the towns, the difference presumably is due to the circumstance that the deaf-mute find better conditions of life in towns and town-like habitations than in rural districts

If two recessively deaf-mute persons marry they must be expected to have only deaf-mute *offspring*. In fact we know several such marriages in which both parents and all the children are deaf-mute. We find exceptions to this

rule, however. Two parents with sporadic recessive deaf-mutism not infrequently have children some, or even all of whom may be normal-hearing. If mistaken diagnoses and illegitimacy can be left out of account, this must be explained either by variation of manifestation, which is unlikely, or by the existence of different genes for recessive deaf-mutism, to which there seems to be no objection.

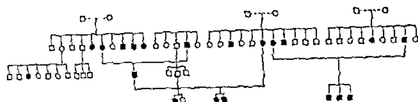


Fig 61.—Family with sporadic deaf-mutism, typically recessive inheritance (after Lindenov)

In conformity with this latter explanation there occurs a special form of sporadic recessive deaf-mutism associated with retinitis pigmentosa called *Usher's syndrome* This disease is presumably due to a polyphenous hereditary unit, which causes both a congenital defect of the organ of hearing resulting in deafness, and also, later in life, a degeneration of the retina. Mental deficiency, and in rare cases hereditary ataxia are occasionally met with in Usher's syndrome

Attention has been called to the fact that the recessive deaf-mutes often are of infantile or dysplastic body type, and it has been claimed that their mental development likewise is somewhat retarded beyond that which could be accounted for safely by the deaf-mutism. The investigations made so far into this question have not given completely reliable results, however

The genetic-hygienic measures to be taken are in the first instance prevention of offspring in the cases of marriage between two recessively deaf-mute, next to advise against consanguineous marriages in these families, and marriage when both partners belong to families in which hereditary deaf-mutism occurs If a recessively deaf-mute marries a person with normal hearing the risk of deaf-mute offspring is small, but the gene will naturally spread in the population If the incidence of recessive deaf-mutism in the population is 0 02 per cent, we may, as stated p 121, calculate that 2 8 per cent of the population are heterozygous for the gene Theoretically there is then 2 8 per cent chance that a person with hereditary deaf-mutism marries a normal-hearing heterozygote

In practice, however, this calculation does not hold good, because the gene for deaf-mutism is not evenly distributed in the population, but is most frequent in families with considerable intermarriage. Moreover, we cannot take it that deaf-mutes choose their partners quite at random; more likely they choose another deaf-mute or one belonging to a family with deaf-mutism. Finally we must, as stated, reckon with the possibility that different genes may produce recessive deaf-mutism.

HEREDITARY LABYRINTHINE IMPAIRMENT OF HEARING OR DEAFNESS. This affection can be either hereditary or acquired. It is localized in the internal ear and most often leads to more or less pronounced impairment of hearing, but rarely to complete deafness. It may be congenital, but as a rule it does not develop and give symptoms till later in life. The characteristic change is a malformation of the cochlear bone associated with defects of the nerve tissue and malformation of the membraneous connective tissue. The disorder is believed to be due to a developmental anomaly. The disease is typically dominant. Severe and early developed cases are often seen side by side with light and late occurring cases in the same family. Concordance is frequent in twins

The lesion may be difficult to differentiate from exogenously produced forms of impaired hearing. Hereditary labyrinthine, impairment of hearing or deafness may in pronounced cases indicate genetic-hygienic measures

Senile impairment of hearing is often a familial character.

OTOSCLEROSIS When hereditary, otosclerosis is a dominant disease. It is twice as frequent in females as in males In the U.S.A it is said to be present in almost 0 2 per cent of the population Just over half of the cases are solitary The otosclerotic impairment of hearing is due to sclerotic processes in the petrous portion of the temporal bone; but if these processes are not found in and around the internal ear, they cause no symptoms Morbid-anatomical examinations have often shown such symptom-free processes It seems to be a matter of chance whether or not they concentrate in such places as to produce stapedial ankylosis and other changes leading to hardness of hearing This is an instructive instance of how variation of manifestation of a hereditary factor may occur. As previously stated, otosclerotic changes are occasionally found associated with blue sclerotics and bone fragility

It is doubtful whether otosclerosis justifies genetic hygienic measures There may, however, be combined medical and eugenic indication for induced abortion, as the disease presumably may be aggravated during pregnancy and lactation.

Otitis media and *mastoiditis* are particularly frequent in certain families. This may have various causes, e g a special structure of the skull, a tendency to tonsillar hypertrophy, sensitive mucous membranes, and susceptibility to certain infections. This question is, however, not yet sufficiently elucidated. One-egg twins fairly often present concordance with regard to otitis media.

An acoustic heredo-degeneration has been claimed to exist in certain families, i e many different ear lesions should occur in these families; but this theory hardly holds good.

MALFORMATIONS. *Microty* (small ears) and anoty may occur as irregularly dominant traits The same is the case with big and outstanding ears and different malformations of the external ear, such as cup-shaped ears, cat ears, flat helix, crus cymbae, and adherent lobe.

Fistula auris congenita, regarded as a vestige of the first bronchial cleft, is irregularly dominant *Congenital atresia auris* may likewise be due to a hereditary factor. Cervical ear has been seen in a very few families. Exostoses in the external auditory meatus may be dominant

In the nose we may find *septal deviations*, concordant in one-egg twins. The defect is dominant. The same applies to *atresia choanae posterior* and *dacrystenosis*, *polyposis nasi*, and *atrophic rhinitis* (*ozoena*).

Congenital laryngeal stenosis occurs in rare cases as a hereditary defect, as do also *laryngospasm*, *laryngeal papillomas* and *fistula colli cong*. The latter abnormality is familial in nearly 20 per cent of the cases

CHAPTER 26

EYE DISEASES

We know of many hereditary diseases of the eye. The eye is easily accessible to examination, has a differentiated structure, and is only subject to a relatively small extent to extrinsic influence.

The incidence of blindness varies from one country to another. At present it is in many countries between 0 05 and 0 06 per cent, and in about half of the cases the blindness is hereditary. It is particularly the exogenous blindness which varies in frequency according to time and place

100 to 150 years ago small-pox was a very common cause of blindness. But in many places this exogenous factor disappeared completely after the introduction of vaccination Trachoma, which formerly was a frequent cause of blindness, gradually recedes as

hygiene advances The same applies to scrofula (gland disease), which by the end of the 19th century often entailed blindness. Gonorrhoeal conjunctivitis in new-born, due to infection from the mother, was until a few decades ago a frequent cause of blindness, but has now disappeared almost completely since the introduction of prophylactic instillation of lapis into the conjunctivae of new-born The incidence of syphilitic keratitis is likewise on the decrease. Xerophthalmia with attending keratomalacia, which previously often caused blindness, is nowadays prevented to a steadily increasing extent by a rich supply of Vitamin A.

About 50 years ago blindness due to corneal destruction constituted nearly 50 per cent of all cases of blindness in Denmark compared with only 5 per cent now.

Hereditary blindness therefore now prevails more than it did previously. Hence impaired vision plays a greater part than total blindness.

TABLE 20.

The frequency of some hereditary eye-diseases.

	Incidence	
	In the population per 100,000 inhab	At birth per 100,000
Congenital aniridia	1	—
Iridochoroidal coloboma	24	—
Congenital hydrophthalmos	8	8
Glaucoma	55	—
Glaucoma intermittens .	46	—
Glaucoma simplex	9	—
Hereditary blindness	30	—
Retinitis pigmentosa	5-20?	—
Partial colour-blindness		
In males	7-8,000	—
In females	440	—
Total colour-blindness	0 3 in an isolate	1 per 100 inhab

ANOPHTHALMOS, ETC *Anophthalmos* is occasionally seen in siblings, whose parents are often related The same applies to microphthalmos. Both defects may occur in the same sibship, and even in one person, who may lack one eye, while the other is abnormally small Both deformities are presumably recessive and may depend on a common gene pair, which may show different degrees of manifestation.

Microphthalmos is generally attended by hypermetropia, but in a few families it is combined with myopia, and inherited as a dominant defect. In a single family sex linked recessive inheritance has been found to be present There seems, in other words, to exist several mutually independent genes which can produce microphthalmos *Microcornea* seems to be recessive or

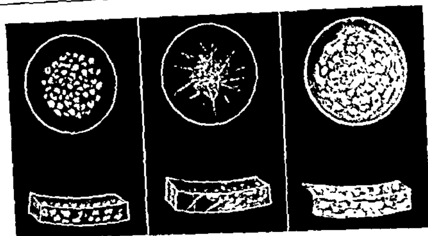


FIG 62—Different types of hereditary progressive corneal degeneration 1) Dominant granular degeneration. 2) Dominant lattice degeneration 3) Recessive macular degeneration (after Sæbø)

in some cases multifactor *Megalocornea* is usually accompanied by good sight. It is supposed to be recessive sex-linked. The mean diameter of the cornea is larger in males than in females As for *macrocornea*, a graded series of size factors with cumulative effects seems to be active in some families

CORNEAL DEGENERATION. Corneal degeneration or dystrophy has also been called corneal *cataract. It may* be congenital or appear at puberty or later. It has been classified mainly into 3 types: 1) One type where the opacities are found scattered over the cornea as small granules It occurs relatively late and rarely leads to pronounced impairment of vision It is dominant. 2) Another type, where the opacities appear as a lattice, is likewise dominant 3) Finally there is found a *third* severer, recessive, macular type, which manifests itself by larger white maculae in the cornea It occurs relatively early in life and gradually impairs the patient's vision so much that the condition approaches blindness The two latter types may lead to blindness, and reproduction should therefore be prevented in some cases

Arcus juvenilis or embryotoxon, opacity of the corneal margin is in rare cases inherited as a dominant defect

DISEASES OF THE LENS Opacity of the lens is far more frequent than of the cornea If cataract is not treated it will gradually lead to blindness, and the results of treatment of early cataract are not too good. Cataract is therefore, together with glaucoma, among the most frequent causes of hereditary blindness.

Cataract may be congenital, infantile, juvenile, or it may develop in middle life, or be presenile or senile. The cataracts are instances of homochronous inheritance, the disease appearing at about the same age in successive generations in the same family.

Cataract may be symptomatic, e g. of diabetes or myotonia atrophica Cataract can be produced experimentally by excess of sugar, deficiency of vitamins, disturbances of the calcium metabolism, or loss of cystine. The opacity which develops is due to precipitation of the proteins of the lens.

In congenital *total cataract* the eye as a whole is defective. Hence the vision is improved but little by operation. *Lamellar cataract,* and in particular *central cataract* are less severe lesions Central cataract occurs in different degrees in different families, and in some cases involves only slight impairment of vision. In dominant *spear cataract* needle- or spear-like crystals, consisting in part of cholesterol, appear in the lens. The inheritance of cataract is nearly always dominant, but recessive pedigrees are known.

Senile cataract was previously believed not to be hereditary. But examinations of old twin pairs have shown that senile cataract is concordant in one-egg twins, with regard to both time of onset, clinical picture, and course. Several types of cataract exist in old people. The mode of transmission of senile cataract is not quite clear. It may be both dominant and recessive. A family with presenile cataract has been observed in which there were found far more affected females than affected males This has been explained as due to dominant sex-linked inheritance.

Cataract is often associated with other eye lesions, such as microphthalmos, ectopia lentis, retinal degeneration, and nystagmus In Sweden Sjogren has described a form of recessive hereditary mental deficiency attended by cataract.

In case of hereditary cataract, in particular the congenital form, genetic-hygienic measures may, of course, be indicated

In connection with an investigation into hereditary cataract attention has been called to the phenomenon designated as *anticipation* or *anteposition* By anticipation we understand that a hereditary disease occurs at a younger age in one generation than in the preceding In a family with cataract the disease occurred in old age in the eldest generation examined, about the age of 40 in the next, about the age of 30 in the 3rd, at the age of 7 in the 4th, and finally almost at birth in the 5th generation Some writers claim to have seen a similar anticipation in the cases of various other diseases, e g glaucoma, schizophrenia, diabetes, and myotonia It is, however, doubtful whether anticipation occurs at all in hereditary diseases, even though it may look as if it does The individuals who have *children are those who are not affected* at a young age Hence we find in the elder generations of the pedigrees chiefly persons affected at a relatively advanced age. In the youngest living generations all are young or children, as are also the affected. The fact might perhaps also be explained in the way that the gene for

cataract in the heterozygous form causes manifestation at a high age and in the homozygous form at a younger age The existence of anticipation has not been definitely proved

Ectopia lentis, dislocation or displacement of the lens, is often congenital, but may also occur during adulthood The defect is generally dominant, in some cases with failing penetrance, but may also be recessive. The direction of the displacement is upward and inward. The condition occurs in various degrees The vision is more or less disturbed It is one of the symptoms in Marfan's syndrome (*vide* p 209), where it then often entails retinal detachment also

The anomalies of refraction, which are very frequent, develop in the main on a hereditary basis. Numerous investigations have been made into their modes of transmission, but these are not yet fully elucidated.

Myopia was previously believed to be due to much reading and other close work, as well as deficient lighting; but this can hardly be the case. Close work is at least not the chief cause of myopia By the 6th year one child out of 1000 is myopic; at 20 years the frequency is thought to be 15 per cent or even higher

Myopia may presumably be due to different genes, of which some show *recessive*, and others irregularly dominant or polymeric inheritance Excessive myopia is generally recessive One-egg twins are highly concordant with regard to refraction, a difference exceeding 2 diopters being extremely rare. The range of variation is narrow The conclusion has therefore been drawn that at least all pronounced forms of myopia are hereditary But evidently the genes for myopia show variability, as also appears from the fact that the two eyes of a person may show highly differing degrees of myopia. There is a certain relationship between myopia and body type. Asthenics are often mildly myopic Excessive myopia is frequently associated with infantile body type. Myopia is in many cases an indication of a general constitutional anomaly It is often aggravated during pregnancy *Retinal detachment*, as a rule in association with myopia, is not infrequently a familial phenomenon Excessive myopia may indicate genetic-hygienic measures

Myopia is much more frequent than hyperopia (= hypermetropia). Only few investigations have been made into the inheritance of hyperopia, which seems to occur in both a recessive and an irregularly dominant form Excessive hyperopia is recessive. The hypermetropic eye is relatively small. Hyperopia generally occurs in infancy It is often associated with microphthalmos, and it is frequent in feeble-minded and Mongolian idiots.

Astigmatism is generally dominant, but a recessive form also exists

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ALBINISM Absence of pigment in the eye is seen in both males and females in case of generalized albinism, which is inherited as a typically recessive trait. The impaired vision attending this abnormality is due not only to photophobia, but also to a defect of the epithelium of the fovea centralis retinae. In addition albinism is often associated with nystagmus, strabismus, or anomalies of refraction Total albinism is rare, but the form limited to the eye alone is even rarer It occurs exclusively in males and is inherited as a recessive sex-linked trait

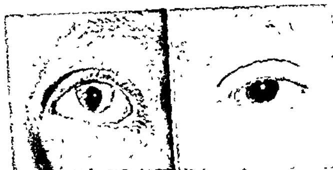


FIG 63—Coloboma of the iris

FIG 64—Aniridia (after Mollenbach)

DISEASES OF THE RETINA. The incidence of *retinitis pigmentosa*, perhaps more correctly designated as dystrophia retinae pigmentosa, has been set at about 0 01 per cent It is a rather common cause of blindness It often comes on in childhood, and it is recessive The parents are related in about 25 per cent Another much rarer dominant form also exists, however, and further, a sex-linked recessive form may occasionally be seen There are thought to be at least 3 genetically different types. In addition, retinal degeneration is one of the symptoms in various syndromes, e g *Usher*'s and *Laurence-Moon-Biedl's syndromes*, and in amaurotic idiocy with epileptic seizures, and in other nervous diseases

In some cases the changes are localized particularly in the macula lutea The hereditary *macula degeneration* usually comes on in childhood, but may manifest itself at any age As a rule it is recessive, but it may be irregularly dominant The senile macula degeneration is dominant Macula degeneration may occur in association with amaurotic idiocy.

Congenital Defects of the Internal Membranes of the Eye. *Aniridia* is a rare dominant defect. The penetrance of the gene is high and the manifestation rather constant. No transitional cases are found between aniridia and coloboma. The incidence of aniridia in the total population is taken to be about 1 : 100,000, and the mutation rate is estimated at nearly 1 : 100,000 Many of the patients suffering from aniridia are of weak intellect. Aniridia involves considerable impairment of vision. Eugenic measures are therefore indicated.

Coloboma of the iris is monocular in about 50 per cent of the cases The vision is generally normal unless the defect is complicated by other anomalies of the eyes, such as hydrophthalmos, cataract, or astigmatism. Most cases occur sporadically, but the defect may be inherited as a dominant trait with varying manifestation

Iridochoroidal coloboma is monocular in about 25 per cent of the cases with equal distribution of the defect on the two eyes. This type of coloboma is often accompanied by other anomalies, such as mental deficiency, deformity of the skull, anomalies of dentition, or congenital heart disease The majority of the cases are solitary Some of the familial cases are dominant, others recessive, and the intrafamilial variation is considerable Most of these patients present pronounced impairment of vision Genetic-hygienic measures are indicated in the dominant cases with impaired vision

Coloboma of the macula is generally not inherited It has been described, however, together with apical dystrophy of hands and feet in one family, and as an irregularly dominant defect in a few families

Heterochromia, i e diversity of colour in the two irides, seems in most cases to be non-hereditary In agreement with this view one-egg twins show discordance But a brown sector in an otherwise light iris of one eye, *iris bicolor*, has in several cases been found inherited as a dominant trait through many generations. It is most frequent in the left eye, and then continues to be inherited as a left-sided anomaly This is peculiar, because most other unilateral hereditary traits may alternate freely from side to side in different generations Poly- and syndactyly may thus in the same family occur unilaterally or bilaterally, on hands or/and feet, and in the unilateral cases almost equally often on either side One-egg twins have also been seen to be concordant with regard to a left-sided dark sector in the iris However, the majority of iris bicolor cases are non-hereditary. It is often seen in only one of the four eyes of a twin pair. Like the mole, it is most likely due to a tendency to accumulation of pigment in patches. In animals the anomaly may be seen to form part of a general piebaldism, which probably is inheritable

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FIG 64—Aniridia (after Møllenbach)

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Hemeralopia is a symptom in many diseases of the retina Congenital night-blindness is dominant. As stated on p. 107, this anomaly has in some families been traceable through about 10 consecutive generations. A form of night-blindness associated with myopia also exists. It is sex-linked recessive. Finally, a third form, combined with excessive myopia, shows simple recessivity. Recessive night-blindness without associated myopia, Noguchi's disease, is common in Japan. Possibly it is sex-linked recessive.

Colour-Blindness.—Several deviations from normal colour vision, trichromacy, are known. Vision may be defective for any of the four primary colours, red, green, blue or yellow, or for all of them The partially colour-blind dichromats fail to distinguish colours either in the red-green (protanopes and deuteranopes) or in the blue-yellow (tritanopes) region of the spectrum and differ in their luminosity curves.

The cones of the retina function in colour vision and in bright light, the rods are mainly sensitive at lower wave lengths and in a dim light. The sensitivity of the cones and rods is related to the photosensitive pigments, iodopsin and rhodopsin As the lens in man is yellow in varying degrees, *aphakic (lensless) individuals are very sensitive to ultraviolet light.*

Total colour-blindness or monochromacy or achromatopsia or day-blindness is a very rare recessive disease. The incidence is probably less than 1 : 100,000 Day-blindness is, however, observed more frequently in isolates, where intermarriage is common On the Danish island of Fuur (1600 inhabitants), for instance, the incidence was formerly 1 per cent, gradually as the isolation of the population was broken up, the incidence of the disease decreased. In the totally colour-blind the cones of the fovea are defective There may, however, also be a cerebral lesion in the region of the lateral geniculate body

Partial colour-blindness is known to be inherited as a sex-linked recessive defect, the gene being present in the X chromosome Red-green colour-blindness is the most common type The frequency in white males is about 8 per cent and *in white females about 0 5 per cent, using Ishiharas test cards* In most other races the incidence is smaller, 1-8 per cent. Some species of animals are totally colour-blind, others have some colour perception

The three forms of defective red-green colour vision, red blindness: *protanopia*, red-weakness: *protanomaly*, and green-blindness: *deuteranopia*, each occur in about 1 per cent of the population, while the fourth form, green-weakness: *deuteranomaly*, is found in 4 to 5 per cent We extremely rarely find defective vision for yellow and blue with preserved normal vision for red and green: *tritanopia* and *tritanomaly*, which may be sex-linked recessive

Red-blindness and green-blindness are each inherited as a sex-linked recessive abnormality, dependent on 2 different series of allelomorphs If a gene for excessive colour-blindness is combined with a corresponding gene for light colour-blindness in the same person, which can only occur in females, the former is recessive to the latter. Protanopia is thus recessive to protanomaly, which again is recessive to normal vision for red If a gene for green-blindness is combined with one for red-blindness in a female, she will not become colour-blind, but her sons will become either green-blind or red-blind. The various degrees of red-blindness and green-blindness are due to 2 different series of allelomorphs The gene for red-blindness can never give green-blindness and *vice versa* The colour-blindness may vary somewhat in degree within the same family; but the main rule is that mild forms occur in some families and excessive forms in others The recessivity of the gene for colour-blindness is not always complete Occasionally we may in heterozygous females see a suggestion of colour-blindness, their colour sensitivity being impaired for the whole spectrum, but particularly for green and bluish green colours In some families we find *colour asthenopia*, i.e. the colour vision is normal on a first view, but speedy tiring results in colour-blindness in a few seconds

THE PRIMARY GLAUCOMA DISEASES Primary glaucoma can be 1) congenital or infantile or 2) adult (juvenile, adolescent or senile).

The Congenital glaucoma or *hydrophthalmos* or *buphthalmos* is somewhat more common in males than in females, and about 25 per cent of the cases are monocular The disease is generally regarded as a result of a developmental anomaly in the chamber angle. Congenital glaucoma is the cause of about 10 to 15 per cent of the hereditary cases of blindness. The incidence at birth, like that in the population is less than 1 : 10,000 The familial occurrence of the disease can be explained by the supposition of recessive inheritance with a manifestation rate in the homozygotes of considerably less than 100 per cent Consanguinity has been demonstrated in the parents of the diseased in more than 10 per cent 2 normal parents who have got a hydrophthalmic child should be made aware of the risk for the succeeding children being affected with the disease Two affected individuals should not have children.

Hydrophthalmos and adult glaucoma must be regarded as two genotypically different diseases

Most cases of *adult glaucoma* are non-hereditary Familial occurrence can be demonstrated in 10 to 20 per cent Adult glaucoma may be simple or intermittent Hereditary glaucoma manifests itself chiefly as an intermittent

glaucoma. The inheritance of glaucoma is irregularly dominant, but in certain cases the disease manifests itself only when provoked by environmental factors. The hereditary glaucoma generally preserves its type in the family, the intrafamilial variation of the disease being small. In adult glaucoma eugenic measures are advisable only where the disease has a decidedly familial, juvenile character (Westerlund).

Optic Nerve Atrophy. Several types of optic nerve atrophy are known, both hereditary and non-hereditary. The hereditary forms vary considerably in course and mode of transmission

Leber's disease manifests itself in adolescence or during adulthood by central impairment of vision, central scotomas, intact periphery of the visual field, and atrophic optic disks. It rarely leads to total blindness Other types may be congenital or come on in childhood and cause complete blindness

Leber's disease is often mentioned as an instance of recessive sex-linked inheritance. It is true that the disease chiefly affects males, though heterozygous females may be affected, too, and that the affected males never have affected offspring; but neither their grandchildren nor any other descendants are affected either The hypothesis has therefore been advanced that the inheritance actually is that of dominance with low manifestation in females, but that the sperm cells containing the gene are not viable About 50 per cent of the sons of the female carriers are affected against only about 8 per cent of their daughters Eugenic measures are unnecessary in the case of the affected male, as he does not transmit the disease. Neither are they indicated for the normal sisters of such males, who have 50 per cent chance of being carriers, as the disease must be considered relatively benign In the cases of affected females eugenic measures may be taken if the woman herself desires it; but if she wishes to become a mother, she should not be absolutely advised against it (Lundsgård).

We have descriptions of families with optic nerve atrophy which show irregularly dominant inheritance, and of rare cases of congenital or infantile recessive optic nerve atrophy, which may be associated with ataxia

Strabismus, Nystagmus, etc *Strabismus* or a squint is rather frequent In Germany the incidence has been stated to be 2 per cent for children and 1 per cent for adults Strabismus seems as a rule to be recessive, but certain forms are dominant, often multifactor In many cases amblyopia is presumably the primary hereditary trait A squint has been found in parent grandparent or siblings in about 50 per cent of squinting propositi

Palpebral ptosis is a dominant defect, sometimes attended by blepharo-

phimosis, epicanthus, and ophthalmoplegia *Ankyloblepharon* may be dominant, in some cases combined with long lower tear duct.

Nystagmus is generally symptomatic, e g. of myopia. It may, however, also be an independent abnormality, which may show either sex-linked recessivity or irregular dominance.

Chapter 27

SKIN DISEASES

As we can examine the skin so easily we know many different hereditary skin diseases, of which only the most important will be mentioned here.

TOTAL ALBINISM Albinism appears to be found in all races, perhaps representing the same gene; but the manifestation rate of the gene varies considerably The incidence of albinism is between 1 :10,000 and 1 :20,000 The most important symptoms of recessive *total albinism*, photophobia and impairment of vision, have previously been mentioned. Albinism being a very rare affection we find consanguinity of the parents of the affected in about *25 per cent of cases* The very conspicuous *partial or circumscribed albinism* is generally *dominant* Localisation and extension, e g piebaldism, white forelock, or spotting, differ considerably in the different families, but may also vary within one family

NAEVI ETC Pigmented naevi, which often are hairy, are not exactly hereditary They may have arisen by somatic *mutation, as* also their asymmetrical occurrence and apparently chance localisation seem to suggest. But the very tendency to moles is presumably *hereditary* The same applies to *lentigines* and *cutiligines* This appears also from comprehensive twin studies, which show that the tendency to such efflorescences *no* doubt is hereditary, but that they show discordance with regard to localisation in one-egg twins.

Freckles, *ephilides*, on the *other hand*, are dominant, and show great concordance in one-egg twins. There is correlation to red or reddish brown hair colour, but freckles seem to be *hypostatic* to dark pigmentation of the skin

Vascular naevi, angiomas, behave in the main like pigmented naevi

The rare skin disease *xeroderma pigmentosum* develops under the *influ-*

glaucoma. The inheritance of glaucoma is irregularly dominant, but in certain cases the disease manifests itself only when provoked by environmental factors. The hereditary glaucoma generally preserves its type in the family, the intrafamilial variation of the disease being small. In adult glaucoma eugenic measures are advisable only where the disease has a decidedly familial, juvenile character (Westerlund).

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Palpebral ptosis is a dominant defect, sometimes attended by blepharo-



Fig 66—Multiple telangiectases in the face

It is irregularly dominant *Cavernous angiomas,* specially in the skin, are likewise dominant, but their sites may vary considerably from individual to individual in the same family

Epidermolysis Bullosa In this affection, where the skin is deficient in elastic fibrils, even a slight knock or pressure will cause the development of bullae under the epidermis The disease is irregularly dominant. A severer affection is the generally recessive *epidermolysis dystrophica,* where the bulla formation takes place in more deep-seated layers, between the cutis and the subcutaneous tissue The latter disease is, furthermore, often associated with defective teeth The severest form of this group of diseases is that called *bullosis connata* or *pemphigus hereditarius,* likewise recessive, where the bullae arise spontaneously The patients die shortly after birth.



FIG 65.—Xeroderma pigmentosum

ence of light and manifests itself first by erythema and conjunctivitis, and later by pigmented areas, white pits, and telangiectasis on the skin It generally comes on within the first year of life and forms scars, in which cancer may develop later, as a rule before the age of 20. Two-thirds of the patients die before the age of 15 The primary cause of the disease is probably a metabolic disorder The inheritance is recessive. *The siblings of affected individuals often present pronounced freckling and naevi, which probably is the heterozygous form of manifestation*

TELANGIECTASIS AND ANGIOMAS Telangiectasis often shows concordance in one-egg twins. *Osler's disease*, in which telangiectasis occurs in skin, mucous membranes, and other tissues, is dominant In *Sturge-Weber's disease* we find *telangiectasis localized particularly on the face and in the cerebrum* Hence this disease is often attended by convulsive fits and mental deficiency

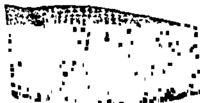


Fig 69—Ichthyosis vulgaris on arm of adult



Fig 68—Ichthyosis congenita Lived 15 hours after birth

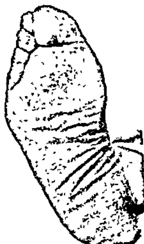


Fig 70—Keratosis plantaris

toms even when present in the recessive form, in other words, also in some of the female family members The inheritance then becomes that of sex-linked irregular dominance The two sex-linked genes, the recessive and the irregularly dominant, are probably allemorphs

Porokeratosis, where the cornification proceeds from the sweat glands, shows dominant inheritance The dominance is somewhat irregular, particularly in females Hence the disease is twice as frequent among males as among females

Darier's disease, psorospermosis vegetans, where cornifications occur round the excretory ducts of sweat and sebaceous glands on the skin, specially in joint furrows and on the abdomen, is a very rare dominant disease Weeping malodorous skin eruptions develop, which highly reduce the patient's possibilities of reproduction Hence the disease is as a rule seen through few



Fig 67—Epidermolysis bullosa

Ichthyosis *Ichthyosis vulgaris* often shows simple dominance. In severe cases eugenic measures may be indicated. In some families, however, the inheritance has been found to be that of sex-linked recessivity Children with *ichthyosis congenita* are often prematurely born and are never viable This disease is recessive

Keratosis, etc. *Keratosis palmaris et plantaris* is a fairly frequent hereditary disease. It occurs in all countries and races It is typically dominant, but must be supposed often to arise by mutation There are also found forms which are not limited to palms and soles, and which show irregular dominance.

Keratosis follicularis or lichen pilaris shows dominant inheritance and concordance in one-egg twins. In two-egg twins and in other siblings it shows great variations. Modifying genes have therefore been supposed to influence its development. A very severe form of keratosis follicularis with cornification of the follicles of the hairs of the head, eyelashes, and eyebrows, is sex-linked recessive. In some of these families the gene occasionally gives rise to symp-

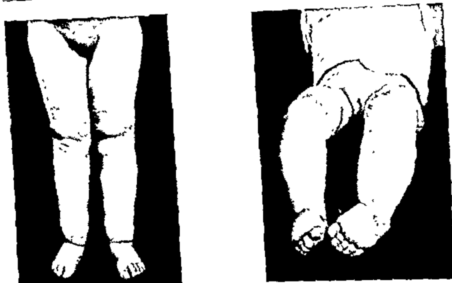


Fig 72.—Chronic hereditary lymphedema (Nonne-Milroy-Meige's disease) in a woman of 41 years and a girl 9 days old Congenital, irregular dominant disease probably due to defective contractility of the arterioles in the subcutis (After Schroeder and Helweg-Larsen).

unaffected relatives have cholesterinaemia, which is therefore supposed to be inherited as a regularly dominant trait and only in some cases accompanied by xanthoma or xanthelasma formations (*vide* p. 256).

Psoriasis Psoriasis, which is a very frequent skin disease, in some families shows typical dominance, while in others the inheritance is less regular Comprehensive family studies showed psoriasis in 8 per cent of the parents of affected, 9 per cent of the siblings, and 13 per cent of the offspring over 30 years of age. These results were obtained without correction for the limited period of manifestation of the disease; in other words, the figures do not indicate the morbid risks in the individual family groups (*vide* p 119). Exogenous factors, e g nutrition, also play a part for the development of the disease, which has been claimed to be related to a disturbance of the lipoid metabolism

Various other skin diseases, besides those already mentioned, e g eczema, urticaria (*vide* p. 259), keloids, and acne, likewise depend more or less on hereditary factors

Some, often very characteristic skin diseases are so rare that they have



Fig 71 —Keratosis follicularis spinulosa

generations only in each family It must therefore be supposed often to arise by mutation.

Epidermoid cysts or *atheromas* or *multiple sebaceous cysts* are dominant, but the gene manifests itself in only about half of the carriers. They may give occasion to genetic-hygienic measures

An- and Hyperhidrosis. *Anhidrosis hypotrichotica* belongs to the defects included under the designation of congenital ectodermal dystrophy. It is often attended by dental defects, defective hairiness, deformity of the skull, and ozaena. It is a rare, as a rule sex-linked, recessive disease In the females of these families we often find dental defects or ozaena alone In a few families the inheritance is dominant In one family several members suffering from congenital anhidrosis developed neurolabyrinthitis between the ages of 35 and 45 *Hyperhidrosis,* localized particularly to the hands and feet, may be due to dominant genes.

Xanthomatosis. *Cholesterosis cutis in association with cholesterinaemia,* manifesting itself either by xanthomas scattered over the skin or possibly by *xanthelasma palpebrarum* alone, is irregularly dominant A number of the

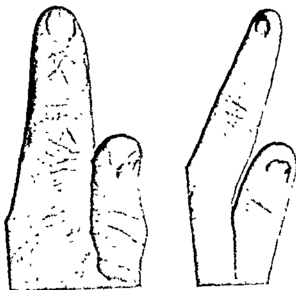


Fig 74 —Onychatrophy in uncle and niece



Fig 75 —Onychogryphosis



Fig 76 —Destruction of nails in epidermolysis bullosa (*vide* p 233).

only been observed in a single family. There is probably no limit to the number of new pathogenetic mutations that may arise in man, but obviously the individual genes differ considerably in stability. Some genes often mutate in a certain way, or at least in a certain direction, thus giving rise to a certain morbid condition, or a series of allelic morbid conditions Other genes mutate extremely rarely, perhaps only once within a measurable period.

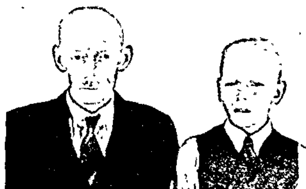


FIG. 73 —Alopecia congenita in father and son It develops during childhood, being therefore not yet total in the son.

HAIR ANOMALIES Baldness, *calvities,* is, if not due to exogenous causes, a dominant anomaly with sex-limitation to men. Twin studies show very great concordance in one-egg twins. Congenital complete or partial absence of hair, *alopecia congenita,* or hypotrichosis, shows dominant inheritance in some families, while in others it is seen only in siblings or as solitary cases The apparently recessive cases occasionally show defective hairiness of the body as well, and at the same time hypoplastic teeth and gryphotic nails *Hypertrichosis lanuginosa,* often attended by dental defects, may be dominant

Premature greyness of the hair, *canities praematura,* is dominant and occurs simultaneously in one-egg twins

A rare hair anomaly is *monilethrichosis,* where the hairs present bead-like enlargement at intervals of about 1 mm It is irregularly dominant Ringed hair, *pili annulati,* is a dominant condition Twisted hair, *pili torti,* is irregularly dominant.

NAIL DEFECTS *Anonychia* and *onychatrophy* may be dominant defects, but are also sometimes seen exclusively in siblings. In some families these abnormalities are associated with patellar defects or other malformations *Leukonychia* may likewise be a dominant trait

a degree of perfection that several congenital heart diseases can now be cured or improved, e.g. ductus arteriosus persistens, aortic coarctation, and Steno-Fallot's disease (Fallot's Tetralogy). A number of these patients, who formerly died before the fertile age, may now be capable of reproduction The chance of spreading the genes for heart diseases has increased, and well-founded eugenic advice is therefore desirable

Acquired cardiac defect rarely shows greater concordance in one-egg twins than in two-egg twins Mitral stenosis is relatively frequent in females of a dysplastic body type. The disease was previously, no doubt wrongly, believed to be inheritable One-egg twins show considerable concordance with regard to the shape and action of the heart. Tachy- and bradycardia, as well as extra systoles may by familial anomalies

It is *difficult* to determine to which extent such a commonly occurring pathological change as *arteriosclerosis* is hereditary. It seems, however, to be a dominant disease Familial occurrence of arteriosclerosis with special localisation, e g to the vessels of brain, kidneys, or heart, may also be observed.

Hypertension is a hereditary disease, presumably related to arteriosclerosis Twin studies have shown that a normal blood pressure must be hereditary, since the two sibs of a one-egg twin pair present a much smaller difference in blood pressure values than those of a two-egg pair. One-egg twins nearly always show concordance with regard to hypertension, although, of course, secondary forms of hypertension may also occur.

Essential hypertension is dominant, but with incomplete manifestation. The morbid risk of hypertension in the population is about 30 to 40 per cent. The age of manifestation within a group of siblings depends on hereditary factors In many families we find accumulation of hypertension, cerebral apoplexy, nephrosclerosis, and heart failure This does not, of course, preclude that extrinsic factors, such as continuous overwork, a strained life, an unvaried high-protein diet, alcoholism, etc , may be of importance as releasing agents Hypertension has been stated to be very rare among primitive peoples, and also comparatively rare in vegetarians Adiposity, chronic alcoholism, arthritis due to defects of uric acid metabolism, and diabetes mellitus occur somewhat more frequently among the relatives of hypertensive propositi than in the average population Eugenic measures are not necessarily indicated in essential hypertension Among cases of hypertension there seems to be a slight preponderance of pyknics, but also many leptosomes have essential hypertension, and many pyknics, even in old age, have a normal blood pressure According to Søbye nephrosclerosis and essential hypertension constitute a genetic entity. The two diseases are phenotypic manifestations of the same gene and may be regarded as different possibilities of development of the same process

In cases of *onychogryphosis* or *hyperkeratosis unguium* the hair is often thin, bristle, and pale-yellow. The defect is said to be relatively frequent in the French population of Canada, possibly on account of emigrants coming from that part of Southern France close to the Pyrenees, where many individuals are found with the same abnormality, the so-called *Cagots.* Onychogryphosis may be a dominant defect

Chapter 28

DISEASES OF INTERNAL ORGANS

Our knowledge concerning the significance of genetic factors in diseases of the internal organs is limited These diseases are rarely congenital, and the question of heredity often cannot be settled except by systematic twin and propositus studies, which have within this field so far been carried out only to a small extent. The following survey of the inheritability of diseases in the internal organs is therefore relatively incomplete.

Cardiac, Vascular, and Pulmonary Diseases. *Congenital cardiac defects* may be hereditary, but are often produced by exogenous factors, as mentioned on p. 194 One-egg twins occasionally, but by no means always, show concordance with regard to such defects as open Botallo's duct or foramen ovale, pulmonary stenosis or the like Furthermore, post-mortem examinations have sometimes revealed familial occurrence of one or the other of these malformations. The incidence of familial occurrence is about 10 per cent Dextrocardia and transposition of the large vessels are seen in the same families Different cardiac defects may be present in the same family, but ductus arteriosus persistens is nearly always, when hereditary, present in all the affected relatives. The inheritance seems as a rule to be recessive, but may, perhaps, be irregularly dominant with low manifestation of the gene. The congenital cardiac defects are often associated with bodily malformations or other severe diseases, such as Mongolian idiocy Eugenic questions occasionally arise in connection with congenital cardiac defects. With our present knowledge it is difficult to give a complete answer to these It is, however, more urgent than in former times to have the significance of hereditary factors for these diseases elucidated. Cardiac diagnosis and cardiac surgery have reached such

philic patients may have a marked tendency to haemorrhage at periods during which the clotting time is only slightly prolonged; reversely, these individuals may have other periods without any tendency to haemorrhage despite a markedly prolonged clotting time

It has been impossible to demonstrate any abnormal properties in vessels or capillaries of haemophilic patients Recently, however, K.-E. Sjolin of the

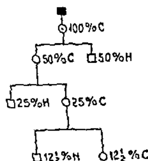


Fig. 77.—Genetic prognosis for descendants of a haemophiliac H haemophilia, C. carrier (after Andreassen)

Copenhagen Institute for Human Genetics, observed changes in the dermal connective tissue obtained by skin biopsies from haemophilics Increased amounts of mast cells were observed, situated mostly perivascularly and containing a sulphuric mucopolysaccharide (related to heparin and the *non*-sulphuric hyaluronic acid) Further, abnormal amounts of mucopolysaccharide, which may possess anticoagulative properties, were present in the connective-tissue ground substance. This finding may *perhaps* explain the tendency to tissue bleeding in haemophilics.

Haemophilia is a typically recessive sex-linked disease. Certain cases of genuine haemophilia have not been observed in females, possibly because homozygous females *are not viable* The sons of haemophilic males are all normal, while all the daughters become carriers of the disease Half of the sons of these daughters become haemophilic Some of the female carriers show a tendency to haemorrhage A daughter of a carrier or a sister of a haemophilic have 50 per cent chance of being a carrier The gene for haemophilia shows little intrafamilial, but *considerable* interfamilial variation In some families we find chiefly severe cases and in others only mild cases But even the least affected individuals *may have* dangerous bleedings.

Various eugenic problems arise in connection with haemophilia A haemophilic will generally be advised against having offspring, but there is hardl

Concordance with regard to *essential hypotension* has been observed in one-egg twins; and dominant inheritance has occasionally been seen.

A disease which may be hereditary, possibly irregularly dominant, is *thrombo-angiitis obliterans* or *Bürger's disease*. It may be concordant in one-egg twins, and in rare cases justify genetic-hygienic measures being advised

Varices, which are exceedingly frequent, are dominant and always concordant in one-egg twins.

Telangiectasis and *angiomas* are often hereditary (*vide* p. 232).

Bronchiectasis occasionally develops from no extrinsic cause, then often manifesting itself already in childhood By the aid of X-ray examination the disease is now diagnosed much earlier and more frequently than formerly. It is nearly always concordant in one-egg twins, and the inheritance is presumably that of irregular dominance Within one family the affected members generally show great similarity with regard to the site and size of the bronchiectasis. Many of the patients present *situs inversus viscerum* or *maxillary sinusitis* as well, the latter probably due to congenital malformation of the maxillary sinus Genetic-hygienic measures may occasionally be indicated in cases of hereditary bronchiectasis

Blood Diseases. *Haemophilia* belongs to the classical hereditary diseases. Its existence has been known since ancient times The disease has occurred in princely families, among others, where it has had grave consequences. The frequency in the population is about 0 002 per cent Haemophilia generally manifests itself within the first year of life. It is most pronounced in childhood and adolescence. Longevity and fertility are greatly reduced. Over one-third of haemophilics die before the age of 20

The most frequent sites of bleeding are the skin, the mucous membranes, the viscera, joints, and muscles and in the nervous system The cause of the bleedings is partly spontaneous and partly traumatic. Characteristic is the oozing haemophilic posthaemorrhage.

Haemophilia is hereditary, but the pathogenesis of the disease is obscure During the past few decades the study of haemophilia has been concerned principally with the process of coagulation and the composition of the blood Great interest has been paid to the blood proteins and this research has led to the discovery of the antihaemophilic globulin, the exact composition and function of which is still unknown

It has been suggested, however, that the pathogenesis of haemophilia cannot be explained exclusively by the altered mechanism of coagulation There seems to be no parallelism between the bleeding tendency of haemophilics and the coagulative changes. For instance, it is a well-known fact that haemo-

in the thrombocytes is greatly reduced, indicating a disturbance of the central functions of the thrombocytes in this disease.

Constitutional thrombopathy. Different forms exist characterized by insufficiency of the thrombocytes, manifesting itself among other ways by a failing agglutinability. Further, a reduced capillary resistance and deficient clot retraction may be found A marked bleeding tendency, particularly from the mucous membranes, is present from childhood. The disease is most frequent in females and may be dominant, in some cases possibly sex-linked dominant.

Afibrinogenaemia, or fibrinogenopenia or *fibrinopenia* may occur as recessive diseases Afibrinogenaemia has been supposed to be the homozygous condition and fibrinogenopenia the corresponding heterozygous form.

Most of these rare haemorrhagic conditions have occasionally indicated that genetic-hygienic measures should be carried out

Morphologically the blood cells may show various hereditary abnormal conditions In *elliptocytosis* the red blood cells, or a large proportion thereof, are elliptic It is an abnormality which seems to persist fairly unchanged throughout life It is often symptomless, but may occasionally be attended by anaemia owing to increased destruction of blood cells, which may cause haemolytic jaundice. The inheritance is that of simple dominance The elliptic blood cells may also be *nucleated*, *kameloid*, likewise a dominant anomaly.

Some hereditary blood cell disorders have a characteristic racial distribution, especially sickle-cell anaemia and thalassaemia

Sickle-cell anaemia is most common in the Negro race, rare in the White race, but less rare among the Mediterranean peoples. No cases of sickle-cell anaemia are known in Mongols and only few in Indians

Sickle-cells are not present in the blood stream but appear when red blood cells are placed in a medium deficient in oxygen, e g in a sealed wet preparation of blood The sickling will gradually increase with time up to 24 hours or more; the cells resemble *sickles, holly leaves etc. It* is fundamentally an abnormality of erythropoiesis

The majority of those affected have no symptoms, they are said to have the *sickling cell trait* or sicklaemia. *But a few* [illegible]

[illegible] called sickle-cell

Patients with sickle-cell anaemia exhibit an asthenic habitus and are subject to haemolytic crises characterized by acute abdominal or joint pains, cerebrovascular symptoms, etc The sickle cells produce thromboses accompanied by severe pains The crisis is relieved when the sickle cells are haemolyzed

indication for genetic-hygienic measures to prevent it. A female carrier is likewise advised against having offspring, and in her case eugenic measures may be indicated. In case eugenic questions arise in connection with a woman who on account of her relationship with a haemophilic has a, say, 50 per cent chance of being a carrier, we can try to make out whether she is one by examining her coagulation time. This can in some cases be done by means of determinations of the coagulation time on unprepared blood according to Bürker's method.

Determination of coagulation time on untreated blood according to Bürker's method (in M Andreassen's modification) Blood is withdrawn by venous puncture (the first 2 to 3 ml are thrown away) and emptied out into a paraffined watch glass 3 or 4 drops are transferred to a non-paraffined dish on water bath at 25° C., and carefully mixed with a few drops of physiological saline without spreading the blood Every 30 seconds a tapering glass rod is passed across from one side of the drop to the other, each time along a new diameter The coagulation begins at lasting displacement of the drop and ends when a fairly large portion of the clotted drop sticks to the glass rod The coagulation normally begins after 4 to 8 minutes and ends after 6 to 10 minutes; it never takes more than 11 minutes It is generally greatly prolonged in haemophilic patients and also somewhat prolonged in many of the female carriers

If then more than 10 to 11 minutes elapse before the blood withdrawn by venous puncture from the woman suspected to be a carrier reaches the stage of complete coagulation, there is reason to believe that she is a carrier. If the coagulation is completed within 10 minutes, she is unlikely to be a carrier and there is no indication for eugenic measures being carried out This determination of the coagulation time is, however, difficult to carry out correctly and requires considerable experience and training.

As haemophilia is a sex-linked disease and we know roughly its incidence as well as the approximate reproductive fitness of haemophiliacs, we have been able to calculate the mutation rate and found it to be about $2{\cdot}5 \times 10^{-5}$

Various other hereditary haemorrhagic conditions exist besides haemophilia.

Essential thrombopenia (thrombocytopenic purpura) displays a temporary or permanent reduction of the number of thrombocytes, as well as a tendency to bleeding from skin and mucous membranes Some cases are hereditary and show dominant inheritance.

Hereditary thrombasthenia. The number of thrombocytes is normal, but these lack the power of producing the enzyme furthering clot retraction. The disease, which is very rare, is stated to be dominant. Recent investigations on patients with hereditary thrombasthenia showed that the nucleotide content

motic resistance of the erythrocytes. The severity of the disease differs considerably from one family to the other, owing to the existence of different types, presumably allelic mutants. Haemolytic jaundice is often associated with other defects, particularly of the osseous system. Cranial deformities, specially turricephaly, are common. Tibial ulcers are also frequent complications Haemolytic jaundice may in severe cases justify eugenic measures being carried out.

Erythroblastosis foetalis was known before 1940 when its aetiology and pathogenesis were discovered The disease had been found to occur relatively often in siblings As, however, consanguinity was not observed particularly frequently among the parents of such patients, recessivity was not considered to be probable Furthermore it had been observed that first-born were more rarely affected than younger members of a sibship. The hypothesis had therefore been advanced that the disease might be due to special traits in the patient's mother, or possibly to protoplasmic inheritance. It had also been noticed that mothers who have erythroblastotic children often were related. The explanation to these apparently mysterious conditions was found by the discovery of the phenomenon designated as Rh incompatibility between mother and child

Numerous hereditary blood diseases exist with anaemia of one type or the other as their main symptom The nowadays rare *chlorosis*, characterized chiefly by hypochromic anaemia with a disturbed iron metabolism, is a dominant disease with sex-limitation to females It also depends largely on environmental factors, however, such as inadequate nourishment and an inexpedient mode of living, and it may be produced by frequent haemorrhages.

An important form of hereditary hyperchromic anaemia is that of *pernicious anaemia*, the incidence of which in the Danish population is barely 0 1 per cent About 30 per cent have relations with the disease within the groups of parents, parents' siblings, siblings, and offspring The incidence is 2 per cent within these groups The morbid risk for the individual groups of relatives have not yet been calculated Nearly 50 per cent of the nearest relations present achylia or subacidity Moreover, relatives of pernicious anaemia patients often display so-called prepernicious blood changes, such as anisocytosis, or paraesthesia Cancer of the stomach is relatively frequent in these families, and also among the patients themselves If these do not die of their pernicious anaemia, owing to liver therapy, cancer of the stomach is a frequent cause of death It has been found that patients suffering from pernicious anaemia generally do not develop their gastric carcinoma in the fundus and upper part of the body of the stomach, where the pathological changes characteristic of pernicious anaemia are localized Possibly the ex-

The sickling phenomenons is observed in about 10 per cent of Negroes in America, and in native Africans most of the groups studied showed an incidence of between 12 and 30 per cent.

The existence of a pathogenetic gene has been assumed, which in single dose elicits the sickling phenomenon and in double dose, sickle-cell anaemia. According to this hypothesis the sickle-cell trait should be regarded as dominant, and sickle-cell anaemia as a recessive character.

Thalassaemia major (from Greek *thalassa* = sea. Anaemia occurring near the sea) or Mediterranean anaemia or *Cooley's anaemia.* The condition is chiefly confined to people living on or near the northern shores of the Mediterranean, or to their descendants in the U.S.A. and other countries. This disease, which is fatal in infancy or childhood, is characterized by severe anaemia with hypochromia, anisocytosis, poikilocytosis, erythroblastosis, leukocytosis, splenomegaly, some hepatic swelling, pigment deposits in the viscera, and an increase of the medullary bone spaces with marrow hyperplasia, as well as thickened cranial bones and mongoloid features

The disease is inherited as a Mendelian recessive In heterozygotes the gene causes a benign form of anaemia, *thalassaemia minor,* first observed in Italy and Italian families in the U.S.A. This condition is characterized by a moderate hypochromic microcytic anaemia, splenomegaly and by symptoms of increased blood cell destruction Thus, the gene is a sublethal recessive, which in its dominant form produces only mild symptoms, comparable with the gene causing sickle cell anaemia, or sicklaemia Both are related to congenital haemolytic anaemia Both major and minor thalassaemia are resistant to all known forms of therapy.

Thalassaemia is probably not confined to the Mediterranean race, but the frequency varies considerably according to people and region In Italy the incidence of thalassaemia minor is between 1 and 10 per cent, in Sicily, for instance, 5 per cent In the Italian population in Rochester, N Y, largely of Sicilian origin, thalassaemia major occurs at a frequency of about 4 per 10,000 births, from which the frequency of thalassaemia minor has been calculated to be about 4 per cent A high frequency of Mediterranean anaemia is found in natives of just those parts of Italy where a high frequency of the blood group R (CDe) is observed The reason for this coincidence is, however, not yet known.

In *hereditary haemolytic jaundice* the red blood cells are spherical and have little osmotic resistance. The disease is dominant It is supposed rather often to arise by mutation, but no calculations of the mutation rate are available. The disease shows great variability. One or more of the symptoms may be absent, e g. jaundice, anaemia, splenic swelling, or the reduced os-

of the population in general, and on one or several genes, which play a part in the localisation of the cancer to the white blood cells and their stem cells Leukaemia seems to constitute a genetic entity, and environmental changes influence the type of the disease. There is evidence that external factors also play a rôle in the development of leukaemia. The probability of the occurrence of several cases of leukaemia in the same family is rather slight; but the risk of cancer in near relatives of a patient with leukaemia is almost 50 per cent.

Congenital reticulosis is a rare recessive disease. The infants die within the first year of life In isolates where this disease occurs, it may add considerably to increasing the infant mortality.

The rare *genuine eosinophilia* has been observed as an irregularly dominant disease

Pelger has described a dominant abnormality of the nuclear forms in the white blood cells It manifests itself by a shift to the left in the blood picture, thus showing relatively few polynuclear and many mononuclear white blood cells A similar blood disease is known in rabbits, having a recessive sublethal effect Most of the homozygous animals die in foetal life, about 10 per cent are born alive, showing skeletal malformations and 100 per cent mononuclear white blood cells (Nachtsheim)

Diseases of Kidneys and Urinary Tract *Glomerulonephritis* is due to exogenous factors in the great majority of cases, but we do occasionally find markedly familial ocurrence with irregularly dominant inheritance. *Orthostatic albuminuria* is also familial in some cases Presumably it is here the underlying lordosis that is hereditary. Different kinds of *malformations of kidneys or urinary tract* (renal hypoplasia, double ureters, etc) have in rare cases been seen as hereditary defects Cystic kidney occurs in a dominant and a recessive form *Congenital cystic kidney*, causing death during or shortly after birth, is recessive The disease is often associated with cyst formation in other organs, such as liver and pancreas, as well as other grave malformations Genetic-hygienic measures may be indicated for the parents when these malformations occur in different combinations in two or more siblings. *Cystic kidney in adults*, generally developing about the age of 40 and often attended by hypertension, apoplexy, or uraemia, is a dominant, but comparatively rare disease *Nephrolithiasis* is often hereditary The cystine calculi seen in cystinuria, which is dominant, also show dominant inheritance. Urate calculi are often present in arthritis urica, and may then occur as a familial trait. Oxalate calculi may show dominant inheritance. We cannot exclude the possibility that uniform habits of life within the same family occasionally may determine the familial occurrence of renal calculi

planation is that both pernicious anaemia and gastric carcinoma result from achlorhydria. Concordance with regard to pernicious anaemia has been seen in a number of one-egg twins. The theory has been advanced that the particular disturbance of gastric secretion which gradually leads to achylia is dominant. In some cases the achylia is then associated with an absence of the *intrinsic factor*. The result is pernicious anaemia, or possibly only funicular myelosis or/and glossitis. These facts are, however, still so poorly elucidated that it is difficult to decide on eugenic measures in connection with pernicious anaemia. Women in particular are, however, comparatively infertile after the disease has developed, even if treated *lege artis*. As a rule it comes on late in life. Female patients with pernicious anaemia have the same chance of surviving as normal females, whereas there is a slightly higher mortality among males.

Constitutional infantile anaemia, due to disturbance of the haematopoiesis, is much rarer than pernicious anaemia. It is a fatal disease occurring in children. It has several times been observed in siblings and scattered in families Hence it is supposed to be recessive. The patients or their relatives often present malformations, e.g. in the urogenital system, or ectrodactyly.

Polycythaemia vera may be recessive, but only few observations are available in support of this theory.

The familial incidence of *leukaemia* has been found to be at least 8 per cent. Several types of leukaemia (acute or chronic lymphogenous or myelogenous, monocytic, or stem cell leukaemia) may occur in the same family. Their relative frequencies are the same for the familial cases as for the disease in general The multiple occurrence of leukaemia in a single family is usually not confined to one particular type Leukaemia therefore probably constitutes a genetic entity Among members of a family there seems to be an age correlation as regards the onset of leukaemia Leukaemia as such is not inherited; but there is an inherited predisposition to the disease. Simple dominance or recessivity may possibly be excluded; it may have a genetic basis with incomplete dominance or homologous polymeric factors (Videbæk).

The incidence of pernicious anaemia is significantly higher among the relatives of patients with leukaemia than among the relatives of the control propositi. This is probably due to a common hereditary predisposition. Among the relatives of leukaemia patients there is a high incidence of cancer as a whole, due to high frequencies of all forms of cancer. Cancer, including leukaemia, is probably a genetic entity dependent on a dominant gene common to all the different forms of "endogenous cancer". The development of leukaemia seems to depend on various conditions, e.g. on a non-specific hereditary predisposition to cancer, which is believed to be present in 20 to 30 per cent

The pituitary body, sexual glands, and the thyroid gland have a particularly great influence on body type and constitution, temperament and personality.

The endocrine disorders are often hereditary. A *familial dyscrinism* has been described with occurrence within one family of different forms of endocrine hypo- and dysfunctions or neuroglandular syndromes, such as dwarfism, sexual abnormalities, adrenal dystrophy, etc. In this connection the existence of a *débilité glandulaire héréditaire* or *insufficientia pluriglandularis* has been suggested. Families have also been reported in which diabetes, Graves' disease, goitre, infantilism, adiposogenital dystrophy, psychosis, neurosis, etc. occur in members of the same family. The endocrine glands, however, do not, either developmentally or otherwise, constitute such an entity that we can speak of definite system diseases or give an explanation of the occurrence of familial dyscrinism.

Most cases of *acromegaly* are solitary, but hereditary cases may also occasionally be seen, which run a mild course and show recessive inheritance.

As previously stated, *anterior pituitary dwarfism* in rare cases occurs as a hereditary disease. A special type attended by adisposogenital dystrophy (described by Hanhart) is typically recessive. *Adiposogenital dystrophy* has been seen in father and son.

Diabetes insipidus is often symptomatic, but may occasionally be hereditary, and then as a rule typically dominant. However, an extremely rare recessive form of diabetes insipidus also exists. In contrast to the dominant form, this does not respond to pituitrin preparations. Finally, a sex-linked recessive form is known, where the heterozygous females, who are carriers, sometimes show mild symptoms of diabetes insipidus.

A number of the diseases of the thyroid gland are hereditary. Goitre and Graves' disease may be due to the same gene, which may probably also produce myxoedema. *Graves' disease* is about 10 times more frequent in females than in males. It no doubt nearly always develops on the basis of hereditary factors, but exogenous factors also play a part in its occurrence. The apparent considerable rise in the incidence of the disease noticed a few years ago might be regarded as evidence in favour of an exogenous influence. This rise is, however, presumably in part due to improved diagnosis, specially owing to more frequent employment of basal metabolism determinations. Among the exogenous factors infection and nutritional or climatic conditions have particularly been considered. Mental trauma hardly plays any rôle, though the disease has a psychosomatic character. Bartels, on the basis of propositus investigations found the following morbidity figures for relatives of patients afflicted with Grave's disease: among mothers 3.5 per cent had Grave's disease and 5.2 per cent goitre, among sisters 8.2 per cent had Graves' disease

Prostatic hypertrophy has displayed concordance in one-egg twins, is most frequent in pyknics, and often occurs as a familial defect. The inheritance seems to be that of irregular dominance, but the question is not yet fully elucidated.

Nocturnal enuresis is in some cases irregularly dominant and concordant in one-egg twins.

DISEASES OF STOMACH, INTESTINES, LIVER, AND PANCREAS. The question of heredity in diseases of the stomach has so far been inadequately investigated One-egg twins generally show concordance with regard to *gastric and duodenal ulcers* or *gastroduodenitis,* also with regard to course, perforation, etc., although, of course, this disease also depends largely on external factors. The inheritance is that of irregular dominance. Gastroduodenitis with or without attending peptic ulcer is to a greater extent a familial disease in young than older people It seems particularly to be associated with the asthenic body type and a nervous unstable temperament. It is the classical psychosomatic disease. It has been a matter in dispute whether the localisation of the ulcer also depends on hereditary factors In some families, however, the site of the ulcer varies considerably from one family member to the other.

Pyloric spasm in children is considerably more frequent in boys than in girls, and nearly always concordant in one-egg twins. It is often a familial affection.

Hirschsprung's disease, megacolon congenitum is irregularly dominant Apparently solitary cases are not infrequent in families, possibly because the dilatation of the colon does not always give characteristic symptoms.

Chronic suppurative coloproctitis is often a familial disease. *Gastro-intestinal polyposis,* often localized in colon and rectum, is frequently dominant

Several hereditary diseases of the liver exist *Familial cholaemia* is believed to predispose to gall-stones *Cholelithiasis* is much more frequent in females than in males and is in many cases irregularly dominant. External factors no doubt also play a considerable part in the development of the disease. There are often found many allergies among the relatives of these patients. *Cirrhosis of the liver* has been seen in siblings and has shown concordance in one-egg twins

Cystic fibrosis in the pancreas has several times been observed in siblings It is probably inherited as a recessive disease.

ENDOCRINE AND METABOLIC DISEASES The internally secreting glands are of importance for the development of the individual from early foetal life, through childhood and adolescence, and further on throughout the adult life

almost equally many male and female diabetics, but after that age the number of female patients rises more than that of male.

The majority of diabetes cases are most likely hereditary. Diabetes mellitus is not a disease, but a syndrome, which does not constitute an aetiological entity. The cause of the metabolic abnormality is to be sought in the pancreas, the pituitary body, or perhaps in an enzyme system, or in the central nervous system During the past few years attention has been drawn to the severe late-diabetic affections developing, despite insulin treatment, in patients with juvenile diabetes, who nearly always die at a fairly young age even if they are given the best treatment

Diabetes is often concordant in one-egg twins Among 98 one-egg twins collected from different series concordance was found in 62 per cent, while only 12 per cent of 176 two-egg twins showed concordance Furthermore, there is often found correlation with regard to the severity of the disease and to the time of onset in twin sibs of one-egg pairs Concerning the time of onset a difference of up to 10 years may, however, be seen. The concordance is therefore the greatest in old one-egg twin pairs, where it is nearly 100 per cent. We not infrequently meet with concordance in the way that one twin of the one-egg pair is a diabetic while the other shows a pathological blood sugar tolerance curve If we leave out of account the discordant one-egg twin pairs where the discordance is due to special external conditions, e g. syphilitic infection in one twin, or the fact that one has been through a greater number of pregnancies than the other, then the concordance with regard to diabetes in one-egg twins is almost complete.

We distinguish between juvenile and senile diabetes, but there is no sharp line of distinction between the two groups Most likely two or more genes exist which can produce diabetes There must be at least one for the juvenile form and one for the senile form, but it is more reasonable to suppose that there is found a series of allelic diabetogenic genes We cannot exclude the possibility either that mutations in quite different places can give rise to disorders of the carbohydrate metabolism which are impossible to distinguish from each other by clinical methods There seems, however, to be a genetic relationship between the different forms of diabetes.

Harris advanced the theory that juvenile diabetes might be due to a gene present in the homozygous form, and that the same gene in the heterozygous form might produce senile diabetes. The conditions are, however, hardly so simple Older theories to the effect that all cases of diabetes depend either on a single recessive gene or an a single irregularly dominant gene have now been abandoned

and 9.7 per cent goitre, and among parents' sisters 2.7 and 3.3 per cent respectively. For normal females the morbid risk of Graves' disease is thought to be 0 5 per cent and that of goitre 1 per cent. The above figures suggest that Graves' disease is recessive with sex-limitation to females and a manifestation rate in these of 70 to 80 per cent.

There is hardly indication for genetic-hygienic measures in the case of Graves' disease. But if one's advice is asked concerning marriage of two Graves' disease patients or one with Graves' disease and one with goitre, such patients will generally be advised against marrying, or at any rate against having offspring, particularly if the couple fear to have children with these diseases. There is 70 to 80 per cent chance that their daughters will have one of the disorders

Sporadic goitre may be either inherited or acquired. In some families we find goitre alone and not Graves' disease. In these families the inheritance is that of irregular dominance with sex-limitation to females *Thyreotoxic adenoma* must be regarded as a toxicosis in an existing goitre. It may therefore, like this, be hereditary or non-hereditary.

Cases of *myxoedema* are generally solitary, but in about 10 per cent they are familial, then showing recessive inheritance. However, as stated above, families are known in which some members present myxoedema, others goitre, and others again Graves' disease Hereditary factors perhaps play a moderate, though not particularly great part in endemic goitre or cretinism The results of twin studies suggest, however, that this disease develops to a large extent independently of hereditary factors.

Addison's disease is occasionally seen in siblings. Post-mortem examinations have in such cases revealed a simple suprarenal atrophy. *The suprarenogenital syndrome* may likewise be seen in siblings This applies to both pubertas praecox, virilism, and hirsutism The parents of children with interrenalism are often related In *macrosomia adiposa congenita,* observed in siblings, we find suprarenal adenoma and adiposity, but not pubertas praecox or hirsutism

The incidence of *diabetes mellitus* is in many countries about 0 4 per cent, e g. U.S A., England, Norway, and Denmark The incidence of diabetes has been rising during the past 50 years or so owing to improved diagnostic possibilities, the increased longevity of the population in general, and particularly of diabetics, as well as the fact that diabetics can now have more children than previously. The frequency of diabetes is highest (2 to 4 per cent) among women between the ages of 60 and 79. The morbid risk is 1 to 5 per cent for males and 2 to 7 per cent for females. The average risk for the whole population has been calculated at about 6 per cent Up to the age of 40 there are

allergic, is involved, causing the paroxysmal character of the disease and the localisation of the arthritis. Hyperuricaemia is due to a dominant gene. This gene lacks penetrance in both sexes, but has a much lower penetrance in females (about 10 per cent) than in males (about 80-90 per cent). Consequently arthritis urica appears as an irregularly dominant disease with frequent skipping, particularly by inheritance through females.

Porphyria is a disturbance in the pigment metabolism through lack of specific enzymes It is a product of abnormal haemoglobin catabolism or more probably a reversion to a more primitive level of pigment formation Porphyrinuria is generally present, and in most cases photosensitivity of the skin and red colour of the bones Porphyria may be congenital or develop in adult patients, in some cases causing paralysis and death. Acute porphyria may be toxic or idiopathic Porphyria is a rare disease. It now and then occurs in siblings or offspring of siblings and is generally recessive or in some families irregularly dominant In *hydroa vacciniforme* the condition of the skin is as in porphyria, but without porphyrinuria The disease is dominant in some families, recessive in others

Haemochromatosis or bronze diabetes, due to a disordered iron metabolism with deposits of haemosiderin in the skin and other tissues, associated with diabetes mellitus and cirrhosis of the liver, may be a recessive disease

Alcaptonuria is due to absence of an enzyme The amino acids phenylalanine and tyrosine are not destroyed in the normal way. Homogentisic acid is excreted in the urine and pigment deposited in the cartilages Ochronosis and arthritis deformans are therefore seen In about half of the cases it occurs sporadically, while the rest are found in siblings The parents being often related, the inheritance is generally supposed to be recessive But there are also found families which show typically dominant inheritance. Ochronosis may occur alone, without alkaptonuria, as a recessive character.

Cystinuria is generally a harmless anomaly Normal people occasionally excrete small quantities of cystine in the urine In rare cases cystine is accumulated in the tissues, and in other cases cystine calculi form in the kidneys The latter condition may be inherited as an irregularly dominant trait, and concordance has been seen in one-egg twins

Endogenous adiposity shows irregularly dominant inheritance.

Progressive lipodystrophy, characterized by progressive disappearance of subcutaneous fat from certain portions of the body or the face, has sometimes been observed in siblings The condition is rare, but seems to be more frequent in Spain than elsewhere.

Dercum's disease or adiposis dolorosa is occasionally seen as a familial condition

Harris, who recently submitted the question to a thorough genetico-statistic investigation found, among others, a slightly, yet significantly higher incidence of consanguinity among the parents of juvenile diabetics than of senile diabetics. Among the siblings of diabetics he found about 4 per cent with diabetes, irrespective of the age of the propositus, and among parents 4 to 8 per cent. The incidence among the siblings of the propositi is higher than stated above, if one or both parents have diabetes. There is little or no correlation between the ages of onset in parents and offspring, but a significant correlation in siblings Bartels and Poulsen recently submitted a small series of juvenile diabetics to a thorough genetic investigation. They found the disease in 12 per cent of siblings, 9 per cent of parents, and 4 per cent of grandparents and parents' siblings, frequency figures which are consistent with the theory of recessivity The frequency of the disease among the offspring of diabetics is not yet known If two diabetics marry, their children will by no means all have diabetes. Steiner found the morbid risk for diabetes among siblings of diabetics to be about 20 per cent and among children about 22 per cent.

Thus, there is no doubt about a greatly increased morbid risk for relatives of diabetics, but it is difficult to answer eugenic questions in connection with diabetes mellitus on the basis of our present experience. We always advise against marriage between two juvenile diabetics and also against consanguineous marriages in families tainted with juvenile diabetes. If a married couple has got two or more children developing infantile or juvenile diabetes, they will be advised against more offspring. In certain cases there is also eugenic justification for advising a patient with juvenile diabetes against having offspring by a normal conjugal partner.

Pentosuria, arabinosuria, and *essential fructosuria* are conditions with no influence on health. Some cases are familial, probably recessive

Renal glycosuria has often been observed as a dominant condition.

Modern biochemical genetics (*vide* p 11) has shown that chemical steps in the synthesis of the various constituents of the living organism and metabolism in general are under genetic control A large proportion of metabolic disorders are caused by the lack of an enzyme, in the absence of which some normal metabolic process fails to appear Some metabolic diseases illustrate, in other words, the relationship between gene and enzyme. Giordano has called these disorders "hereditary enzymopenies"

Arthritis urica or *gout* is more frequent in males than in females and depends to a considerable extent on habits of life and nutrition. It is primarily a metabolic disease with hyperuricaemia Another aetiological factor, possibly

allergic, is involved, causing the paroxysmal character of the disease and the localisation of the arthritis Hyperuricaemia is due to a dominant gene. This gene lacks penetrance in both sexes, but has a much lower penetrance in females (about 10 per cent) than in males (about 80-90 per cent). Consequently arthritis urica appears as an irregularly dominant disease with frequent skipping, particularly by inheritance through females.

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The diseases involving *lipoidosis* are rare, in some cases hereditary affections characterized by accumulation of lipoid in the tissues, with special affinity to the reticulo-endothelial system, and lipaemia. They comprise the following diseases:



FIG 78—Lipodystrophia progressiva

Xanthomatosis with accumulation of cholesterol and cholesterol esters in the tissues It is attended by hypercholesterolaemia

Genuine essential hypercholesterolaemia is due to a dominant gene. About half of the individuals with hypercholesterolaemia present no other symptoms, while the other half suffer from manifest xanthomatosis In nearly all the patients with xanthomas the deposits are present in the tendons. About 50 per cent have palpebral xanthelasma Extensive xanthomatous eruptions on the skin, xanthoma tuberosum, and the very large xanthomas in the tendons are rare.

Angina pectoris, coronary sclerosis, and sudden cardiac death are rather

common among patients with manifest xanthomatosis. The disease is not related to a particular type of constitution. Pyknics are, however, alleged to present higher serum cholesterol values than leptosomes.

Hand-Schüller-Christian's disease manifests itself by accumulation of cholesterol, particularly in the reticulo-endothelial tissue, as well as osseous changes, specially of the skull owing to deposit of xanthomatous tissue with

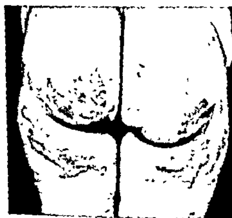


Fig 79—Xanthoma formations on the buttock of a woman, 24 years old Serum cholesterol 462 mg %

areas of decreased density, seen in a X-ray, and dyspituitarism It is irregularly dominant

Gaucher's disease, or idiopathic splenomegaly, is characterized by accumulation of the cerebroside cerasin in the cells, particularly in the reticulo-endothelial cells. It is twice as frequent in males as in females and shows recessive inheritance. Cerasin accumulates chiefly in the spleen, liver, and bone marrow, forming characteristic Gaucher's cells, large, round or polygonal cells full of vacuoles.

Nieman-Pick's disease is marked by accumulation of phosphatides, specially lecithin, in the reticulo-endothelial system, chiefly in the spleen and liver, as well as in the brain Characteristic lipoid-containing cells, so-called foam cells, may be found in all tissues The disease, which seems to occur particularly among Jews, is probably recessive. It occurs chiefly in siblings and is concordant in one-egg twins It is most frequent in girls

Closely related to this disease are *infantile* (Tay-Sachs' type) as well as *juvenile, amaurotic idiocy* (Spielmeyer-Vogt's type), both recessive In these

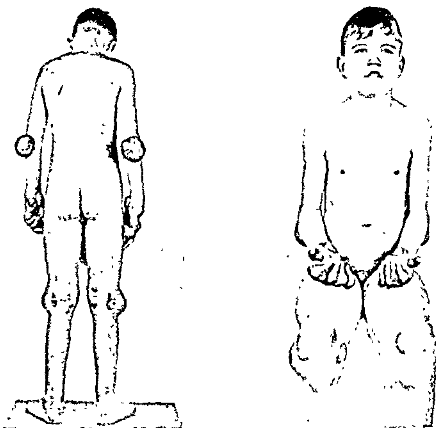


FIG. 80.—Familial Xanthomatosis in a boy 13 years old Monstrous xanthomas in skin and tendons Hypercholesterolaemia (Figs 79 and 80 after Kornerup)

diseases sphingomyelin is accumulated in the cells, particularly those of the brain and the retina, thereby causing idiocy and blindness

Gargoylism, likewise a congenital hereditary lipoidosis, has been described p. 212

In *glycogenosis, v. Gierke's disease*, or congenital hepatonephromegaly, the glycogen metabolism is disturbed, large amounts of glycogen being accumulated in the organs, specially in the liver and kidneys The patients presumably lack a glycolytic enzyme. Other signs are lipaemia and hypercholesterolaemia, inhibition of growth, bone fragility, and adiposity The patients die young. The disease is sometimes seen in siblings and has therefore been supposed to be recessive

The occurrence of *rickets* depends to no small extent on hereditary factors. It shows pronounced concordance in one-egg twins. The tendency to the disease is inherited as a dominant character, and the site is often the same in all affected members of the same family.

ALLERGIC AND RHEUMATIC DISEASES The allergic diseases are due to an antibody-antigen reaction. Four typically allergic diseases, which are genetically related, are: *bronchial asthma*, *vasomotor rhinitis*, *hay fever*, and *Besnier's prurigo*. *Urticaria* and *Quincke's oedema* are no doubt likewise allergic dis-



FIG 81 —Glycogenosis, v Gierke

eases Many other diseases have with more or less justification been claimed to be allergic, e.g. migraine, eczema, and certain other skin lesions, enteral allergies, Menière's disease, cholelithiasis, arthritis and rheumatism, and epilepsy Allergic reactions may occasionally be of importance in the development of many of these diseases, but they are not genetically related to asthma or urticaria Allergic conditions can no doubt be produced in anybody by intense sensibilisation, but in general this occurs only where a hereditary predisposition is present In the case of bronchial asthma and related allergic diseases this predisposition is due to an irregularly dominant gene, which manifests itself only if the predisposed individual is exposed to the action of the necessary allergens within the age period of susceptibility to such action Asthma depends in addition on a hereditary localisation factor.

The rule is that the same form of allergy predominates within one family, often in the way that the various members show the same reaction to different allergens But there are many exceptions to this rule. The strength with

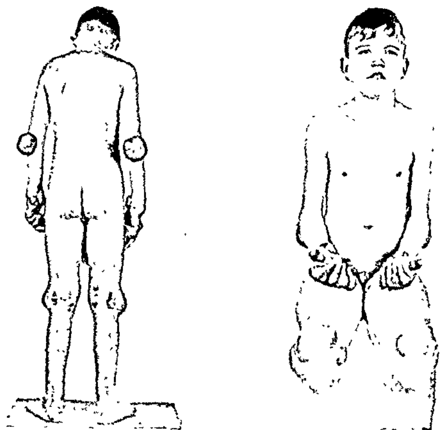


FIG. 80—Familial Xanthomatosis in a boy 13 years old Monstrous xanthomas in skin and tendons, Hypercholesterolaemia (*Figs 79 and 80 after Kornerup*)

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ditary cases are irregularly dominant. This applies to spondylitis deformans and malum coxae senile, as well as to arthritis deformans in other joints.

INFECTIOUS DISEASES Susceptibility or predisposition plays a considerable part in infectious diseases. Resistance and immunity reactions depend in a large measure on hereditary factors. The resistance of a population must in the general be regarded as approximately the same from year to year On the other hand, a shift may no doubt occur in the susceptibility of a population to a certain infection, due, for instance, to a change in its power of resistance depending on hereditary factors. The individuals who are killed by the infection, e g during epidemics, are chiefly those who only have little resistance to the infection in question Provided the low power of resistance is a hereditary trait a selection will gradually occur, and the population will become increasingly resistant from generation to generation This will manifest itself by a change in the character of the disease towards greater benignity Various infectious diseases may in this way gradually become milder

In a population where a tuberculous infection, for instance, has persisted for a considerable length of time, homologous polymeric genes, which increase the resistance to tuberculosis, must be supposed by selection little by little to rise in number If therefore, by hygienic measures, an infectious disease, such as tuberculosis, gradually becomes practically rooted out from a population, it must be feared that the population's resistance to this disease is *reduced in the* course of time and that therefore it will become extremely susceptible if exposed to *another* tuberculous infection It is reasonable to suppose that the same applies to other infections

This is in agreement with the experience often made that a fresh infection coming to a population that has long been spared the disease *often runs* a very severe course This applies not only to venereal diseases and tuberculosis, but also to generally benign infections, such as measles, whooping-cough, influenza, etc, which may assume the character of extremely severe epidemics with a high mortality This fact has been observed all over the world The cause may be that the populations concerned *are not immunized* and that their hereditary resistance to the infectious disease in question is low

Though depending to a great extent on hereditary factors the resistance is also determined by other conditions, in the first instance by previous latent or manifest infection

Immunity depends, of course primarily on extrinsic factors, but the ability to produce antibody is unquestionably in no small measure due to hereditary factors Thus, the ability to produce diphtheria antitoxin varies greatly f

which the symptoms manifest themselves is also most often nearly the same in all affected members of one family, though rather considerable intrafamilial variation may occur.

Hay fever with attending conjunctivitis is in 10 per cent of the cases associated with asthma One-egg twins show marked concordance with regard to this disease, though generally one twin reacts to more allergens than the other.

In *bronchial asthma* a hereditary predisposition is nearly always seen, and other allergic diseases, such as rhinitis or prurigo, are frequent in the family. *But external conditions are also of great importance in the development of* this disease, as appears, for instance, from the fact that one-egg twins show little concordance

It is doubtful whether migraine can be regarded as an allergic disease. We may in the same family see a hereditary predisposition to migraine and possibly also to proper allergic diseases. One-egg twins show marked concordance with regard to migraine

The rheumatic diseases depend to a rather considerable extent on hereditary factors. In about one-third of the cases of *rheumatic fever* other patients with the same disease are found in the family, apparently without this being due to a common infection or other uniform extrinsic influence The predisposition to rheumatic fever is inherited as a recessive character As might be expected, rheumatic heart disease is also often a familial phenomenon in families with rheumatic diseases

Primary progressive polyarthritis and *secondary chronic polyarthritis (rheumatoid arthritis)* are likewise both familial They not infrequently occur in families with many cases of acute rheumatic infection *Spondylarthritis ankylopoietica* is frequently found in the same families Stecher and others conclude that ankylosing spondylitis is due to a dominant factor with about 70 per cent penetrance in males and about 10 per cent in females The incidence is about one case in 2,000 of the adult population In some sibships the penetrance is almost complete in both sexes, this seems especially to be the case when at least one sister has ankylosing spondylitis The disease may be a consequence of a deficiency in ACTH or some other substance which is genetically controlled

Heberden's nodes, or osteo-arthritis of the fingers, are about ten times more common in females than in males. Idiopathic Heberden's nodes show a definite hereditary pattern. It is probably due to a sex-influenced dominant gene with higher penetrance in females than males

The deforming mono- and polyarthritis (osteoarthritis, arthrosis) cases depend largely on hereditary factors, as evidenced by twin studies The here-

ditary cases are irregularly dominant. This applies to spondylitis deformans and malum coxae senile, as well as to arthritis deformans in other joints

INFECTIOUS DISEASES. Susceptibility or predisposition plays a considerable part in infectious diseases. Resistance and immunity reactions depend in a large measure on hereditary factors. The resistance of a population must in the general be regarded as approximately the same from year to year. On the other hand, a shift may no doubt occur in the susceptibility of a population to a certain infection, due, for instance, to a change in its power of resistance depending on hereditary factors The individuals who are killed by the infection, e g during epidemics, are chiefly those who only have little resistance to the infection in question Provided the low power of resistance is a hereditary trait a selection will gradually occur, and the population will become *increasingly* resistant from generation to generation This will manifest itself by a change in the character of the disease towards greater benienity Various infectious diseases may in this way gradually become milder.

In a population where a tuberculous infection, for instance, has persisted for a *considerable* length of time, homologous polymeric genes, which increase the resistance to tuberculosis, must be supposed by selection little by little to rise *in number* If therefore by hygienic measures, an infectious disease, such as tuberculosis, gradually becomes practically rooted out from a population, it must be *feared* that the population's resistance to this disease is reduced in the course of time and that therefore it will become extremely *susceptible if* exposed to another tuberculous infection It is reasonable to suppose that the same applies to other infections

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Though depending to a great extent on hereditary factors the resistance is also determined by other conditions, in the first instance by previous latent or manifest infection

Immunity depends, of course, primarily on extrinsic factors, but the ability to produce antibody is unquestionably in no small measure due to hereditary factors Thus, the ability to produce diphtheria antitoxin varies greatly from

individual to individual. The same applies to animals. Some horses are excellent antitoxin producers, while others produce only very little antibody. Complement, of such great importance for bacteriolysis, is completely absent in some guinea-pigs, while in others it is abundantly present. Total lack of complement has been shown to be inherited as a simple recessive character. The ability to be a good producer of diphtheria antitoxin is inherited in guinea-pigs, presumably as a dominant character.

The case in man seems to be similar. The ability to react positively or negatively to Schick's diphtheria toxin test is no doubt in some measure hereditary. Two Schick-positive parents have chiefly Schick-positive children, while two Schick-negative parents have chiefly Schick-negative offspring, provided, of course, the exposure to latent and manifest infection is the same in both groups. Family investigations into the Schick reaction have revealed that in man the ability to produce antitoxin depends on an incompletely dominant gene.

We may distinguish between individual, racial, and species susceptibility to infectious diseases. The susceptibility of species is so well-known that no instances need be mentioned. In animals, where we have relatively pure races, an unquestionable racial susceptibility has been observed Such has also been claimed to exist in man Mongolians show only little susceptibility to scarlatina, Indians to cholera, and Jews to tuberculosis It is, however, doubtful whether this difference is due to the presence of specific genes in the individual races Many different factors may assert themselves. We know no instances of complete resistance of some races to certain infectious diseases

Thus individual susceptibility to different infectious diseases varies very considerably, presumably under the influence of hereditary differences However, these questions need further investigation They have so far been best elucidated through twin studies

Though over 90 per cent of the population get *measles*, this disease shows somewhat greater concordance in one-egg twins than in two-egg twins The same applies to *whooping cough*, which likewise is very frequent In *scarlatina* we find a fairly pronounced familial uniformity with regard to sequelae *Diphtheria*, specially the severe forms, shows a marked familial accumulation, which *must be supposed in part to be due to a hereditary susceptibility* Of such a relatively rare disease as *poliomyelitis* we occasionally see several cases at widely different points of time within the same family.

Angina tonsillaris and *catarrhal infections* also show some familial accumulation One-egg twins display very pronounced concordance with regard to acute tonsillitis; and a familial uniformity may be seen regarding such sequelae as nephritis, polyarthritis, and endocarditis

The question of heredity in *tuberculosis* has been fairly thoroughly studied. The significance of a predisposition to tuberculosis is definitely recognizable. Before the discovery of the tubercle bacillus tuberculosis was regarded as a familial disease. It is a common experience that some people may be exposed to massive infection over long periods without falling ill, while others, who have been exposed to only a slight danger of infection, get the disease.

Through twin studies we have obtained a suggestive picture of the significance of a susceptibility to tuberculosis. Among one-egg twins the ratio between concordant and unquestionably discordant pairs with regard to severe tuberculosis is 9:1, while among two-egg twins the corresponding ratio is 1:41. This great difference is evidence in favour of the importance of hereditary factors for the development of tuberculosis The markedly familial occurrence of tuberculosis is thus not due exclusively to uniform exposure to infection and conditions of life within the same family. There must be supposed to exist a specific hereditary predisposition to tuberculosis, dependent on one or more hereditary factors, presumably a series of homologous polymeric genes.

Tuberculosis has, in other words, two main causes, the tubercle bacillus and the specific hereditary predisposition to the disease However, various modifying factors, hereditary as well as non-hereditary, also influence the occurrence and course of the disease

As previously stated, it is not the immunity as such which is *inherited*, but the greater or smaller ability to produce antitoxin The passive immunity present during the first few months of life and due to transmission of antibodies from the mother through placenta or mother's milk, cannot be regarded as hereditary.

We can hardly be justified in speaking of hereditary infectious diseases They can be transmitted through the placenta or by contagion during or shortly after birth, but are hardly direct transmissible with the sperm cells or egg cells We know no certain cases of germinative infection A *syphilis héréditaire* accordingly does not exist; but we must bear in mind that congenital syphilis may produce uniform symptoms in various members of the same family which therefore mistakenly may be regarded as hereditary

TUMOURS The different types of tumours (meaning neoplasms), benign or malignant, are more or less dependent on a hereditary predisposition For the development of the various neoplasms endogenous and exogenous factors interact in an intricate manner. Tumours occur in all living beings, their formation is a common biological phenomenon

A tumour is a character involving growth, the development is a result of a chain or a physiological complex of processes directed by both environ-

mental and genetic factors. Malignant cells have an unlimited capacity of *growth and division Cancer is a problem of disorganized growth. In the* normal ontogeny quite a number of organizers (or evocators or inductors) are known, originally dependent on genic action, and producing their morphogenetic effect in different stages of development. The biochemistry of several of the organizers is known; some of them are sterols related to oestrogenic and carcinogenic hydrocarbons This is why genetics, embryology and biochemistry are brought together in the study of carcinogenesis.

Tumours are abnormalities of development, which cause differentiated and mature cells to return to an undifferentiated state with frequent cell division, irregular mitoses, asymmetrical, and multipolar, polyploid and polytene cells.

In the precancerous and cancerous cells the nucleoli are large with a high nucleic acid and protein production. Ribose nucleotides, concerned with protein production, are abundant in precancerous tissue, being necessary for their conversion into desoxyribose nucleotides required for the rapid multiplication of cell nuclei Supposedly cancerous tissues are more sensitive to irradiation *than normal tissues owing to their higher content of desoxyribose nucleic acid.*

Somatic carcinogenic cell mutation may result from a relationship between plasmagenes and chromosomal genes and be caused by irritation of the tissue or by a specific virus Tumour cells and their host can both undergo mutations affecting the susceptibility, which for each particular tumour depend on a series of inherited differences

In animal experiments it is possible by continued inbreeding to produce strains where all or nearly all the animals die of cancer. On the other hand, we may also by sufficiently intense exposure of the animals, i e by painting with carcinogenic hydrocarbon, produce cancer in 100 per cent of the animals.

Tumours arise from genetic changes of particular cells The specific properties of a tumour can be transmitted from one animal to another through a constant lineage of cells by transplantation

Various twin studies have been made on different cancer forms. They show that cancer more often is concordant in one-egg twins than in two-egg twins. But discordance is also often seen in one-egg twins. The presence of cancer in one such twin need not necessarily imply that the other will likewise get the disease. As far as can be judged from the limited material available, cancer, when concordant in one-egg twins, seems often to be of the same type and to attack the same organs in both twin sibs

A patient, who by surgical or *radiological treatment has been cured of*

cancer, is supposed, apart from the risk of metastases, to have a relatively great chance of developing another cancerous growth.

Most of the hereditary benign tumours are inherited as monomeric dominant or incompletely dominant characters.

Tuberous sclerosis or *epiloia* is a congenital developmental anomaly, a dysneoplasia, characterized by tumour-like malformations in various organs or organ systems, such as the brain, retina, skin (especially adenoma sebaceum), liver, heart, lungs and kidneys. The mode of transmission is that of dominance with greatly varying manifestation and intrafamilial variability. According to Borberg it is hardly possible to calculate the mutation rate because of marked phenotypical variation. The incidence in population is about 0.001 per cent

Genetic-hygienic measures are advisable for patients suffering from tuberous sclerosis. If normal individuals have a child with the syndrome the eugenic advice will depend on the result of a family investigation If there is no evidence of latent inheritance, mutation is the most likely explanation, and it can hardly be justifiable to advise against more offspring.

Recklinghausen's neurofibromatosis is a congenital developmental anomaly characterized by tumour-like formation, particularly in the skin and nervous system The disease occurs in all races and the incidence has been roughly calculated at 1:2000 in the general population and 1:200 among mental defectives In the peripheral syndrome the picture is dominated by cutaneous tumours and pigmentations But this may be associated with a central syndrome with cerebrospinal manifestations The disease is irregularly dominant with great intrafamilial variability, but in most cases the peripheral syndrome is found to be of a similar type with that seen in a neurofibromatosis-affected parent Inheritance through phenotypically normal parents is also observed There seems to be a hereditary predisposition to the development of the central syndrome If apparently normal individuals have a child with neurofibromatosis this may, as in tuberous sclerosis, be due to mutation or to latent inheritance (Borberg)

Eugenic advice must be given in conformity with the above-mentioned rules for the inheritance of the disease

Tuberous sclerosis and neurofibromatosis are mutually independent diseases due to two different genes

Many other non-malignant tumour forms exist, which, like the two mentioned above, are found scattered as many small tumours in various organs (phacomatoses) Some of these are:

Multiple lipomas, which are irregularly dominant

Angiomatosis of retina and cerebellum, found in the cerebellum and, more rarely in the medulla oblongata and medulla spinalis (Lindau's disease) and in the retina (v. Hippel's disease). It has in some families been observed as a dominant disease. It is in some cases associated with cyst formation in the

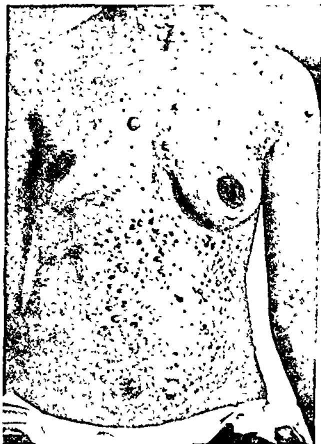


FIG. 82 —Neurofibromatosis

kidneys and pancreas, as well as with the presence of a hypernephroma The three latter affections may also occur together as a familial phenomenon

Scattered vascular tumours, *telangiectasis* and *cavernoma,* are mentioned p. 232.

Multiple exostoses, enchondroma, and *enostoses* are mentioned p 213

Fibroma molluscum as well as *fibroma plantae* are dominant

Atheromas and *multiple sebaceous cysts* are both irregularly dominant In rare cases eugenic measures are indicated here. Other tumour-like skin lesions are mentioned in the chapter on skin diseases

Renal cysts with multiple cysts in several organs are mentioned on p. 249 and goitre on p. 251.

Teratomas and *ovarian dermoids* are in rare cases familial, and twin births are relatively frequent in these families. They were previously regarded as a distorted foetus They may, however, possibly be due to a disorder of the various organizers in embryonic tissue.

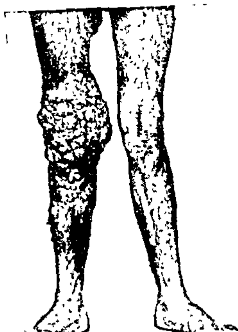


Fig 83 —Neurofibromatosis

Melanomas and *melanosarcoma* of the choroid have been seen in siblings, and have also been observed through 3 generations The extent to which melanin granules accumulate in the melanoblasts of man as well as the patterns caused by these granules in the skin are determined by genetic and environmental factors The abnormal pigmentation plays a part in various hereditary diseases, which have already been mentioned, e g albinism, neurofibromatosis, retinitis pigmentosa, naevi, and *xeroderma pigmentosum* The latter affection is recessive, but, as previously mentioned, also dependent on exogenous factors, especially the influence of light and ultraviolet rays It may be reckoned among the precancerous conditions In this group we may also include *gastro-intestinal polyposis* and possibly *achlorhydria*

Glioma retinae or *retinoblastoma* is a hereditary malignant tumour, which is congenital or develops in infancy or early childhood in one eye or both.

The incidence has in Holland been calculated to be 1 in 34,000 live births, and the tumour is binocular in 20 per cent. Recessive inheritance is unlikely, because consanguinity is not particularly frequent among the parents. The disease must therefore be supposed to be due to a dominant gene with rather low penetrance. Solitary cases are, however, very often seen; only 1 out of 50 to 100 patients have affected relatives A few families plainly show dominant inheritance Persons who have had one eye removed in childhood owing to retinal glioma have been observed to have several children with the same disease. Hence patients operated on for retinal glioma ought not to have children The morbid risk is low for siblings of children with the disease. Hemmes examined 211 siblings of 48 patients with retinal glioma and found that none of these siblings developed the disease Some of the sporadic cases have possibly arisen by mutation.

Like certain sarcomas, retinal glioma often develops early in life, in contrast to carcinoma, which occurs in middle-aged and old individuals.

Glioma cerebri has often been seen in siblings. Other intracranial hereditary tumours, such as acoustic tumours and cerebellopontile angle tumours, which may cause deafness and blindness respectively, should in many cases be included under neurofibromatosis. Bilateral acoustic tumours have been observed to cause deafness in a family through 5 generations.

Little is known as yet of the heredity and incidence of *cancer*. The results of cancer statistics differ somewhat from one country to the other. In 1943 the Danish Cancer Registration Centre noted 131 cancer cases (including lymphogranulomatosis and leukaemia) per 100,000 inhabitants Of these, 20 cases were breast cancer, 4 cases leukaemia, and 20 cases cancer of the uterus Of the latter cases three-quarters were localized in the cervix, and one-quarter, or 5 per 100,000 inhabitants, in the body These figures were obtained by inquiries directed to all physicians and hospitals of the country, *but naturally did not include all the cases occurring in the population.*

Breast cancer depends on hereditary factors, and the tendency to this particular form of cancer is bound up with an inherited predisposition to endogenous cancer *in general The development of "endogenous cancers"* is probably due to a general hereditary predisposition The site of the tumour is determined either by hereditary or external factors. In many pedigrees the general hereditary predisposition appears to be inherited as a dominant character. External factors are not particularly important in the development of breast cancer (Jacobsen).

The inheritance of *cancer of the uterus* has been studied. *Cancer of the cervix* seems mainly conditioned by exogenous factors. *Cancer of the body*

depends on a general gene for cancer common to cancer of all sites ("endogenous cancers"), but probably also on a localization factor in which one or several genes may be concerned (Brobeck).

Other forms of cancer in man likewise in some cases occur as familial diseases, e g *cancer of the stomach* and *cancer of the rectum*. Other forms again, such as skin and lip cancer, seem to depend only little on hereditary factors In *cancer of the oesophagus* the same disease is often found in a close male relation. In these families, however, the patients with cancer of the oesophagus are often chronic alcoholics It is probably a tendency to alcoholism, and not to cancer, which is inherited

Tumour-causing factors To summarize our present knowledge concerning tumour-causing factors we must distinguish between 1) endogenous factors and 2) environmental factors

1) *Endogenous factors* Among the endogenous factors the most important is the hereditary predisposition, which varies for tumours of different forms, sites, and types The hereditary predisposition is divisible into

a *A* general predisposition, probably irregularly dominant or multifactor.

b A localisation tendency due to localisation genes, organ factors or depending on the histological structure

A hereditary variation occurs in susceptibility or refractoriness to tumour formation or tumour transplantation

Somatic mutation and cytoplasmic inheritance must be taken into consideration

2) *Environmental cancer-causing factors* may be divided into

a. Internal milieu, including individual, type, race, or species, and internal cancerogenic environment, caused by hormonal imbalance and metabolic disturbances, nutrition, age, and intoxication

b External milieu, or exogenous factors, including irritation from injury, chemical, thermal, or ray influence, parasites, bacteria, and viruses

Viruses as the direct cause of tumours, which is common in fowl, have comparatively rarely been observed in mammals (the milk factor in mice or Shopes papilloma in rabbits) and never in humans

Eugenic measures are rarely considered in connection with cancer. But it is useful to know that certain cancer forms depend on a hereditary predisposition, as *this* may in some cases result in earlier diagnosis and treatment of the tumours

Chapter 29

NERVOUS DISEASES

Epilepsy is the most frequent hereditary disease of the nervous system. It is probably due to intermediary metabolic disorders in the brain cells or changes in the course of the action potentials in the resting brain. Other metabolic disturbances, e.g. certain lipoidoses, likewise manifest themselves as nervous diseases Some nervous diseases are associated with developmental anomalies or universal tumour formation. A large group of hereditary nervous diseases are found among the heredodegenerative or abiotrophic forms. The abiotrophic diseases are allegedly characterized by a progressive destruction or premature wearing out of certain organs or parts of organs Occurrence of destructive pathological changes in an organ at a certain point of time will naturally result in early failure of this organ, and the same will happen in case of hypoplasia of the organ.

Epilepsy Epilepsy is characterized by attacks of loss of consciousness with (grand mal) or without (petit mal) attending convulsive seizures. Local convulsions, usually without loss of consciousness, are known as *Jacksonian or* cortical epilepsy.

Epilepsy is either cryptogenic (syn. idiopathic, essential) of unknown aetiology, or symptomatic, due to injury, tumours, infections, toxaemia, or arteriosclerosis

The incidence of epilepsy in the population is 0 3 to 0.5 per cent.

Cryptogenic epilepsy is hereditary in some cases, while in others it must be supposed to have an organic cause, which, however, cannot be disclosed by clinical methods of examination. Symptomatic epilepsy may run a course exactly like that of the cryptogenic form

In cryptogenic epilepsy no coarse anatomical changes are found in the brain But in the great majority (about 90 per cent) of epileptics there are changes in the electro-encephalogram (EEG) In normal people the EEG most often *shows regular rhythmic waves, thus differing from that of the* epileptic both in rate and amplitude of electric disturbances. The latter registrates an intermittent powerful discharge of a relatively high voltage (*dysrhythmia*). The discharge may occasionally, particularly in children, have the character of spike-and-wave formations In the average population 5 to 10 per cent show dysrhythmia, while only very few (0 5 per cent) present spike-and-wave formations in the EEG.

Twin studies on epileptics have given somewhat differing results The concordance of one-egg twins with regard to cryptogenic epilepsy is presumably more than 70 per cent and is observed not only with respect to seizures, but also with respect to the type of seizure (grand mal, petit mal or psychomotor) and to electroencephalographic pattern. About 10 per cent of one-egg twins show concordance with regard to symptomatic epilepsy. As for the EEG, there is nearly 100 per cent concordance in normal one-egg twins, but only 5 per cent in two-egg twins Lennox, Gibbs, and Gibbs, on the basis of EEG investigations on epileptic twins and in epileptic families, concluded that the pattern and the frequency of cortical electric waves are hereditary traits, and that the dysrhythmia probably may be inherited as a dominant character. Persons with dysrhythmia possess a predisposition to convulsions, and a certain percentage of these reach above the convulsion threshold and thus have epileptic attacks, partly owing to their dysrhythmia and partly due to environmental factors This hereditary form of epilepsy often begins in childhood with petit mal, later to develop into convulsive fits The disease generally manifest itself between the 5th and the 20th year.

Investigations into the empirical genetic prognosis based on propositi suffering from epilepsy have given varying results according to the type of epileptics used as propositi If the epileptics whose relatives are examined are chiefly out-patients (Alstrom) we find a lower hereditary taint than if we start by examining institutional epileptics (Harvald) Older investigations (Conrad), presumably based on institutional propositi belonging in the main to the low classes of society and probably comprising some mentally deficient epileptics, showed a relatively great hereditary taint, with epilepsy, mental deficiency, psychopathy, etc among the relatives of epileptics

Harvald (1951) estimated the empirical genetic prognosis of epileptics with the following result · Epilepsy is found to occur in 4 per cent of the children and siblings, and in 3 per cent of the parents of cryptogenic epileptics. Oligophrenia occurs in 3 per cent of the children and in about 1 per cent of siblings Criminality is one and a half times as high among the children and siblings as in the average population

In symptomatic epilepsy about 1 per cent of the siblings are affected with epilepsy and 1 per cent with oligophrenia

The relative fertility among patients with cryptogenic epilepsy is about 60 per cent of the average, lower among males than among females

Epilepsy must be regarded as a physical disease with no relation to neurosis Its appearance is independent of mental trauma The epileptic change of character is probably mainly to be regarded as a consequence of the process underlying the dysrhythmia, which also plays a part in the development of

Chapter 29

NERVOUS DISEASES

Epilepsy is the most frequent hereditary disease of the nervous system. It is probably due to intermediary metabolic disorders in the brain cells or changes in the course of the action potentials in the resting brain. Other metabolic disturbances, e.g. certain lipoidoses, likewise manifest themselves as nervous diseases. Some nervous diseases are associated with developmental anomalies or universal tumour formation. A large group of hereditary nervous diseases are found among the heredodegenerative or abiotrophic forms. The abiotrophic diseases are allegedly characterized by a progressive destruction or premature wearing out of certain organs or parts of organs. Occurrence of destructive pathological changes in an organ at a certain point of time will naturally result in early failure of this organ, and the same will happen in case of hypoplasia of the organ.

Epilepsy. Epilepsy is characterized by attacks of loss of consciousness with (grand mal) or without (petit mal) attending convulsive seizures. Local convulsions, usually without loss of consciousness, are known as Jacksonian or cortical epilepsy.

Epilepsy is either cryptogenic (syn. idiopathic, essential) of unknown aetiology, or symptomatic, due to injury, tumours, infections, toxaemia, or arteriosclerosis.

The incidence of epilepsy in the population is 0.3 to 0.5 per cent.

Cryptogenic epilepsy is hereditary in some cases, while in others it must be supposed to have an organic cause, which, however, cannot be disclosed by clinical methods of examination. Symptomatic epilepsy may run a course exactly like that of the cryptogenic form.

In cryptogenic epilepsy no coarse anatomical changes are found in the brain. But in the great majority (about 90 per cent) of epileptics there are changes in the electro-encephalogram (EEG). In normal people the EEG most often shows regular rhythmic waves, thus differing from that of the epileptic both in rate and amplitude of electric disturbances. The latter registrates an intermittent powerful discharge of a relatively high voltage (dysrhythmia). The discharge may occasionally, particularly in children, have the character of spike-and-wave formations. In the average population 5 to 10 per cent show dysrhythmia, while only very few (0.5 per cent) present spike-and-wave formations in the EEG.

of getting it, if they reach the age period of manifestation. If one grandparent is known to have the disease, while both parents are unaffected, but under 25 years of age, the children have 25 per cent chance of falling ill

Patients with Huntington's chorea ought never to have offspring, but they have often had children before the disease has manifested itself. Eugenic measures, e g. induced abortion, are sometimes indicated in cases of individuals who are still unaffected, but whose father or mother have the disease. It is

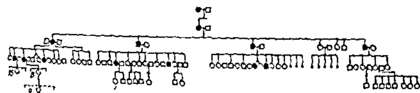


Fig 84—Huntington's chorea. The patient marked 1, who was 20 years old, was submitted to induced abortion at eugenic indication (after Sigurd Petersen)

impossible to say whether an individual of a tainted family will get the disease until the symptoms manifest themselves. The EEG is normal in latent carriers Haldane has pointed out that selection probably is taking place in favour of late onset in Huntington's chorea, since those with early onset are unlikely to marry This is perhaps due to an effect of modifying genes (*vide* p 64)

Hepatolenticular degeneration with bilateral changes of the lenticular nucleus and cirrhosis of the liver, is presumably recessive, occurring in siblings But, although the disease is extremely rare, increased consanguinity among the parents of the affected has not been demonstrated. *Pseudosclerosis* (Westphal-Strumpell's or Wilson's disease) is closely related to progressive lenticular degeneration Its mode of transmission has been studied systematically in experiments on rabbits and found to be typically recessive.

Paralysis agitans or *Parkinson's disease* is characterized by atrophic changes in the ganglion cells of the corpus striatum According to Mjones, the age of onset varies between 7 and 81 years, average 49 years The disease is not particularly rare In about 40 per cent of the cases other instances of the disease are demonstrable in the family In the familial cases the inheritance must be supposed to be that of irregular dominance with a manifestation rate of about 50 per cent A considerable variability of symptoms is found. The solitary cases presumably comprise cases of both hereditary and exogenous origin An increased number of cases of Parkinsonism and cerebral arteriosclerosis with associated Parkinsonism is found among the relatives of patients

epileptic dementia. The latter is, however, also an after-effect of the attacks and a consequence of the drug treatment.

The view has been advanced that epilepsy occurs perhaps particularly among individuals of the athletic body type; but this has not been proved. Under the social conditions nowadays existing in all Northwestern European countries cases of epilepsy are fairly equally distributed throughout all the social classes.

The indication for eugenic measures in cases of cryptogenic epilepsy must be determined *in each individual* case. Systematic employment of geenral measures, such as sterilisation and prohibition of marriage, are of course, not justifiable Electro-encephalographic examination of the patient and his nearest relations can often be of guidance in eugenic problems. If the EEG *of one or both conjugal partners shows dysrhythmia of the epileptic type the* chance that the offspring will get epilepsy is not inconsiderable

Epilepsy alone is not sufficient eugenic indication for induced abortion or sterilisation of the patient Because of the social and psychic derogation of the patients, and their choice of mate among tainted families, eugenic measures are in many cases warranted when there are additional reasons for their being carried out (*vide* p 308).

Recently (1951) Lennox wrote, "A transmitted predisposition to seizures and brain damage are each (or both) important factors in the origin of a person's epilepsy. A constitutional cerebral dysrhythmia may, among other things, be the visual representation of a predisposition to seizures Advice regarding marriage and children must be individualized" Furthermore he mentioned that "the laws (now happily moribund) of 14 of the American States are forbidding marriage of the epileptic, and even threatening fine or imprisonment for any who assist"

Narcolepsy may be hereditary, and is then irregularly dominant and variable in its expression It is not really related to epilepsy, but is due to disturbance of the pituitary body and adjoining regions of the midbrain.

DISEASES OF THE EXTRAPYRAMIDAL SYSTEM *Huntington's chorea,* due to degeneration of the ganglion cells, not only in the corpus striatum, but also in the cortex itself, is probably always hereditary It rarely manifests itself till between the ages of 25 and 50 (mean age 35-36, and the average duration of the disease is 13 to 14 years). It is a very grave disease with its violent choreatic movements, disturbances of speech, and progressive dementia. It is not particularly rare. The clinical picture varies somewhat from one family to the other, and may also vary rather considerably within the same family.

When one parent has the disease 50 per cent of the children have a chance



FIG 87.—Myotonia hypertrophica Thomsen's disease

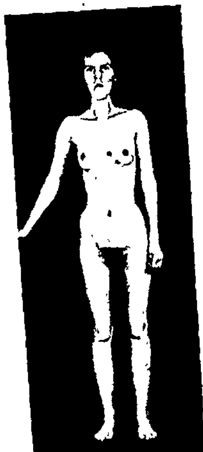


FIG 88.—Myotonia atrophica (dystrophia myotonica) (Figs 87 and 88 after E. Thomasen).

OTHER HEREDITARY NERVOUS DISEASES *Progressive muscular dystrophy* is in many cases hereditary It occurs in different forms with different modes of transmission The facioscapulohumeral form is dominant, while the scapulohumeral form often occurs sporadically The form affecting the lower extremities, by far the most frequent, is inherited as a recessive affection with sex-limitation to males This form has also been alleged to be sex-linked recessive, but this can hardly be correct. Many cases which clinically are indistinguishable from the hereditary are no doubt acquired This can be shown by muscle biopsy and electromyography. The acquired cases may be due to polymyositis or myopathia thyreopriva (H Levison)



Fig 85—Hepato-lenticular degeneration (after H C Hall)



Fig 86.—Progressive muscular dystrophy. Marked atrophy of deltoid and pectoral muscles

with paralysis agitans Possibly Parkinsonian syndromes of varying nature occur in families with a hereditary susceptibility of the extrapyramidal system

Dystonia musculorum deformans, tends to be familial The same applies to *athetosis*. One of the cerebral palsies, *Little's disease*, or *paraplegia spastica cerebralis*, is often due to birth injury, but a developmental defect seems to be of basic importance in some cases. *Familial spastic paralysis* is sometimes hereditary.

Tic may be hereditary. But in the individual cases it is often difficult to say whether it is of the functional or the striatal type.

Myoclonic epilepsy, the classical recessive disease, was described as such in 1913 by H. Lundborg in a large Swedish farming family with 2,232 members in seven generations and with a high incidence of intermarriage The disease showed typical recessivity. In the family there were found, besides, many nervous and mental diseases, as well as 9 cases of paralysis agitans Myoclonic epilepsy is an extremely rare disease accompanied by progressive dementia and cachexia.

Several striatal diseases are often found accumulated in the same family. *Chorea minor* is also frequently present in these families, indicating that the basal ganglia are a *locus minoris resistentiae* and therefore susceptible to the rheumatic infection.

atrophy It is generally recessive; but in some families the inheritance seems to be dominant, especially where the disease occurs in a mild form.

We distinguish between two forms of hereditary ataxia. *Spinal ataxia, Friedreich's disease*, is recessive or irregularly dominant. It most often manifests itself in childhood, but may also come on later in life *Cerebellar ataxia, Marie's disease*, as a rule does not begin till adult life It may be dominant



Fig 89 —Infantile progressive muscular atrophy (Werdnig-Hoffmann) in 5 months old girl Extreme universal hypotonia (After S Brandt)

often irregularly so Both forms may justify genetic-hygienic measures being carried out

Nothing certain is known of heredity in *syringomyelia* It has been stated to occur particularly in families where the so-called status dysraphicus is found, characterized by funnel chest, kyphoscoliosis, spina bifida, and various other abnormalities The question of heredity in *disseminated sclerosis* is just as uncertain as in syringomyelia Hence there is generally no basis for genetic-hygienic measures

Migraine, often dominant, is described among the allergic diseases

Familial periodic paralysis shows a frequency of 0 0008 per cent and a morbid risk of 0 003 per cent The inheritance is irregularly dominant.

Trophoneurosis of hands and feet may be a familial affection.

Diffuse cerebral sclerosis is rare It is occasionally seen in siblings and is

There is indication for eugenic measures in the dominant facioscapulo-humeral form, even though it runs a rather benign course. The form affecting the lower extremities is more malignant. Genetic-hygienic measures must here be taken as in the cases of other recessive diseases. *Myopathia distalis tarda* is inherited dominantly.

Congenital hypertrophic myotonia, Thomsen's disease, was first described by the Slesvig physician Thomsen as a typically dominant disease in a large family with offshoots in Denmark, Norway, and Holland. In other families the inheritance is more irregular. In addition, we know several families, described by E. Thomasen, among others, with simultaneous or alternating occurrence of the severe *atrophic myotonia* (syn *myotonic dystrophy*) and cataract. The disease is dominant. The fertility being reduced the disease as a rule persists through two or three generations only. It justifies genetic-hygienic measures

Like the myotonias, the hereditary muscular atrophies are much rarer than the muscular dystrophies. *Neural muscular atrophy* is somewhat more frequent in males than in females, and is often dominant, occasionally skipping a generation. The disease may also occur in solitary cases, or only in siblings, where then it runs a relatively severe course A distinction has been made between 12 different biotypes of this hereditary disease. *Spinal muscular atrophy* may be recessive and occurs now and then in two or more siblings Different forms exist. one comes on between the ages of 25 and 30; another, infantile, form (Werdnig-Hoffmann) often occurs as early as the age of 12 months (see below); a third form is that of bulbar paralysis; a fourth form, amyotrophic lateral sclerosis is often attended by a certain spasticity *Charcot-Marie-Tooth's disease* is a dominant, distally localised spinal muscular atrophy

Infantile progressive muscular atrophy (Werdnig-Hoffmann) (previously sometimes called myatonia congenita Oppenheim) is a fairly rare recessive disease. Consanguinity is common in the parents of the diseased No conspicuous intrafamilial variability has been observed, but some interfamilial variability is present, the disease running a more rapid course in some families than in others. Concordance in identical twins has been reported several times. Vitamin E deficiency may possibly play a part in the occurrence of the disease. The inherited defect may thus be conceived to consist of defective absorption or utilisation of this vitamin. This theory finds support in observations from animal experiments, but has not yet been confirmed clinically. Most of these patients die within the first years of life; very few reach the age of 15 to 20 years Genetic-hygienic measures may be warranted in married couples who have had one or more children with the disease.

Spastic spinal paralysis runs a far less severe course than neural muscular

viceable, though not ideal, basis for employment of eugenic measures within the field of psychiatry.

OLIGOPHRENIA. The exact number of mental defectives cannot be indicated It varies with time and place, specially that of patients with exogenous mental deficiency (comp p. 218). Many borderline cases exist, and the diagnosis is

TABLE 21

Frequencies of mental defects and diseases affected by heredity, and of alcoholism and criminality (in Denmark, from Fremming and Strömgren, vide p. 121)

	Incidence	
	In the population per 100 000 inhab	Morbid risk per 100 000
Feeble-mindedness	1,300	—
Hereditary cases	1,000	—
Non-hereditary cases	300	—
Mentally retarded	1,700	—
Psychopathy	3,000	—
Schizophrenia	300	900
Manic-depressive psychosis (both sexes)	—	1,640
In males	—	1,020
In females	—	2,240
Alcoholism	1,700	—
Criminality, 15-55 years		
In males	—	2,800
In females	—	610
Total psychosis expectation up to 55 years	—	4,100
Mentally abnormal, evt periodically, 10-55 years	—	12,000

difficult to establish Amentia is as much a social concept as a medical one. Amentia has been defined as a state of incomplete development of such a kind and degree that the individual is incapable of adapting himself to the normal environment in such a way as to maintain existence independently of supervision, control or external support The following incidence figures are based on intelligence tests and are to be regarded as approximate only. The true mental defectives probably constitute 1 to 2 per cent of the population. About 0 1 to 0 2 per cent are idiots (I Q 20-35), almost twice as many imbecile (I Q 50-55), and the rest feeble-minded (American, morons) (I.Q. 55-75) To these may be added several mentally backward or dull, retarded or simpletons (I Q. roughly 75-90) A distinction has also been made between 1) mild or high-grade mental defectives (I Q over 50) and 2) severe or

therefore supposed to be recessive; exogenous factors, however, also play an important part in the aetiology of diffuse sclerosis. It often comes on in infancy and in most cases runs a rapidly lethal course. According to Strömgren *et al.* diffuse sclerosis is genetically related to other diseases, e g. hereditary spastic spinal paralysis, disseminated sclerosis and certain neuropsychiatric abnormalities, and osseous malformations. A spinal form of cerebral sclerosis, *Pelizaeus-Merzbacher's disease,* occurring chiefly in males, is more chronic. We cannot say whether the inheritance is that of irregular dominance with sex-limitation, or that of sex-linked recessivity.

Alzheimer's disease is a severe form of presenile dementia with diffuse and disseminated degenerative processes in the cerebral cortex, in some families irregularly dominant.

Chapter 30

MENTAL DISEASES AND OTHER MENTAL ABNORMALITIES

Mental affections is the group of diseases for which hereditary factors are *of the greatest practical importance. An immense number of comprehensive* genetic investigations have been carried through in psychiatry.

The normal mental characters each depend on many genetic factors and are highly modifiable by extrinsic influence The inheritance of mental abnormalities cannot either be expected to be perspicuous. Most likely at least some of them depend on single pathogenetic genes, but the effect these produce on the background of the total psyche is not always directly recognizable. A great number of reactions may precede the phenotypic manifestation, which cannot be followed through all its stages. In analysing human behaviour either hereditary or environmental factors alone will be found to be determinative.

To this may be added the uncertainty of psychiatric diagnosis The individual types of diseases are difficult to define, and hardly ever constitute aetiological entities.

In spite of the great work done within the study of psychiatric genetics we still do not know the exact inheritance of a single one of the most common mental diseases. However, through comprehensive propositus investigations figures have been procured for the morbid risk in the different family groups which render possible an empirical genetic prognosis. This affords a, yet ser-

logical entity It will possibly in the course of time be divisible into genetically independent subgroups.

There is a gradual transition from normal intelligence through mental backwardness to feeble-mindedness, which probably in some cases is to be regarded only as an extreme variant of the normal psyche, while in others it has been produced by specific pathogenetic genes (single major genes or chromosome abnormalities). The former cases, representing not so much defective conditions as abnormal primitive states, are probably due to continued negative selection. In these cases the mental deficiency must, indeed, be regarded as hereditary, not monomeric, however, but as a multifactor, graded character (polygenic). There is, in other words, a biological relationship between true mental deficiency, weak intellect, and the various stages of backwardness This appears plainly from numerous family investigations In addition, however, there are the proper pathological forms of mental deficiency Lewis distinguished between 1) sub-cultural defectives, to be regarded as normal variants, and 2) pathological defectives, to be regarded as abnormal variants.

In the forms of mental deficiency showing monomeric inheritance the genetic prognosis can, of course, be made on the basis of Mendelian laws. But these forms are comparatively rare In the great majority of cases we must employ the existing empirical figures They must, however, be accepted with some reservation, partly owing to lacking aetiological entity, and partly because the existing empirical material has been collected by many different workers (Brugger, Juda, and others), whose principles of classification of mental defectives differed somewhat

Among siblings of mental defectives (hereditary form)

63-94 per cent are affected when both parents are mentally deficient
33-41 „ „ „ „ „ one parent is mentally deficient
13-18 „ „ „ „ „ neither of the parents are mentally deficient

The above percentage figures are fairly reliable. Various investigations have given similar results. Regarding the children of mental defectives, irrespective of whether they have mentally deficient siblings, we find the following.

62-78(90?) per cent mentally deficient children if both parents are mentally deficient
about 30 „ „ „ „ „ „ one parent is mentally deficient

Among other relatives of patients with hereditary mental deficiency we find

medium- or low-grade mental defectives (I.Q. under 50). In America the designation feeble-minded is frequently used equal to mental defective.

The results of family investigations gave the impression that mental deficiency *may* be *inheritable*, but an exact estimate of how often this is the case was procured by twin studies. They showed that 50 to 80 per cent of all cases are hereditary, chiefly the mild and the moderate forms, but idiocy may also be inherited. The non-hereditary cases are due to extrinsic causes, such as birth injury, possibly intracranial haemorrhage during or immediately after birth, premature birth, twin birth, head injuries, infection, or intoxication, maternal sensitisation, and nutritional effects, in short damaging of brain tissue *pre-, intra-, and postnatally, most often within the first years of life*, at any rate before the age of 6. Even acquired cases of mental deficiency develop particularly when a predisposition is present, as appears from the fact that relatively many oligophrenics are found among the relatives of patients with exogenous mental deficiency.

Mental deficiency is thus most often congenital or develops during the first few years of life, after which it remains fairly unchanged. Some cases, *especially mild ones, may, however, undergo a certain late development during* or after the age of puberty.

Oligophrenia may constitute part of a more complicated syndrome, or be associated with some physical abnormality; or it has the character of progressive dementia, occurring as a concomitant sign in organic nervous diseases (e.g. myoclonic epilepsy, Friedreich's ataxia, dystrophia myotonica, amaurotic idiocy, and some forms of retinitis pigmentosa) or other more general affections (tuberous or diffuse cerebral sclerosis, neurofibromatosis, congenital myxoedema, cretinism, keratosis follicularis, Sturge-Weber's disease, and gargoylism) where the central nervous system is involved. A number of these diseases may, as previously stated, show monomeric recessive or dominant inheritance.

Uncomplicated mental deficiency may also in some families be inherited as a *monomeric, recessive, autosomal or sex-linked defect*. This was demonstrated by Sjogren in different isolated districts in Sweden. He investigated certain forms of rather pronounced mental deficiency, each of which constituted a clinical entity. One form was attended by cataract and small stature. According to Sjogren, amaurotic idiocy is also typically recessive.

Some cases of mental deficiency are, however, more probably dominant. Possibly, some of the mild forms are dominant and the severe forms recessive, but many rare recessive genes are also supposed to exist which can give rise to a high-grade deficiency. The consanguinity rate is raised among parents of mental defectives. Hereditary mental deficiency does not constitute an aetio-

logical entity. It will possibly in the course of time be divisible into genetically independent subgroups.

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The above percentage figures are fairly reliable Veri-

62-78 (90?) per cent mentally deficient children if both parents are mentally deficient	
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Among other relatives of patients with hereditary mental deficiency we find

8-30	per cent	mental	defectives	among	children of	siblings
12-14	„	„	„	„	„	cousins
5-30	„	„	„	„	„	grandchildren

These figures are of uncertain value, as different investigations show great variations. Roberts, Penrose, and others found a correlation between mental defectives and their siblings with regard to I.Q. of about 0.5, that is, *the mean* intelligence of siblings is about half way between that of the propositi and normal intelligence. A considerable correlation with regard to I.Q was also found betwen mental defectives and other groups of relatives, e.g mothers, half-siblings, first cousins, and nephews and nieces. In the case of mothers it exceeded 0 5.

Wildenskov has made a comparative investigation among relatives of two groups of mental defectives comprising 50 propositi each. One group consisted of high-grade mental defectives (children in a school for mental defectives) and the other group low-grade mental defectives (asylum patients). Among siblings of the school children 22 per cent were mentally deficient and 29 per cent mentally backward, while in the case of the asylum patients the corresponding figures were 8 and 18 per cent respectively

In addition he found that no matter whether both parents were backward, feeble-minded, or imbecile about 90 per cent of their children were mentally deficient. Hence it is important to note weak intellect in families with mental deficiency when making a genetic prognosis. This is in agreement with the results of Penrose's investigations of brothers and sisters of 1280 mental defectives, as shown in Table 22

It applies to a certain extent that the same degree and form of mental deficiency is inherited in the same family; but this is by no means always the case. In some families all grades of mental deficiency are seen among siblings or offspring no matter whether the propositi are backward, feeble-minded, or imbecile In particular there are nearly always many mentally backward members in families with hereditary mental deficiency

The fertility of the feeble-minded may be very high, both intra- and extramatrimonially, owing to their often unchecked sexual desire Reliable figures are not available for elucidation of this fact, but its significance has no doubt been exaggerated Nowadays confinement in an institution and special care, in connection with an increased knowledge of methods of birth control in all social classes contribute towards checking the fertility of mental defectives. Nevertheless we still find feeble-minded and backward individuals with many children. Defective mothers are more frequently observed than defective fathers. Among idiots there is almost complete absence of effective fertility. With imbeciles reproduction is possible, but rare

A fact of great eugenic importance is the assortative mating of mental defectives Oligophrenics do not mix freely in the population The saying that birds of a feather flock together applies to them more than to others. This adds to the value of genetic-hygienic measures.

TABLE 22.

Percentages amongst sibs of 1280 mental defectives (after Penrose cit Fraser Roberts).

Grade of proposita	Grade of sibs				
	Normal (or superior)	Dull (Backward)	Feeble-minded	Imbecile	Idiot
Dull (Backward)	77.4	16.2	4.9	1.0	0.5
Feeble-minded	76.8	11.9	8.3	2.5	0.6
Imbecile	83.5	7.6	4.6	3.5	0.7
Idiot	81.0	9.9	4.2	1.7	3.2

Mental deficiency is the affection where eugenic measures are most often required, and where negative eugenic measures, such as sterilisation, segregation, and prohibition of marriage are most often employed. Mental defectives ought not to have offspring, those with inherited mental deficiency for eugenic reasons, and those with acquired deficiency because they are unable to provide for and educate their children, even though they can bear normal children. In case a normal pregnant woman desires induced abortion, there is usually sufficient indication for such if she has previously born one or more children with hereditary mental deficiency Otherwise we must in each individual case make the genetic prognosis on the basis of the stated empirical figures and take genetic-hygienic measures *accordingly*.

Various clinically specific forms of mental deficiency exist, of which the following will be mentioned.

Mongolian idiocy, or *mongolism*, is present in 0.02 to 0.03 per cent of the population and in about 0.15 per cent of new-born, almost equally often in boys and girls Nearly all the signs of Mongolian idiocy indicate retarded development The mortality rate is very high. Mongolism practically always occurs as solitary cases in the families. It has, indeed, sometimes been observed in siblings and other relatives of Mongolian idiots, but hardly more often than that it can be explained by chance sampling This affection is therefore believed to be non-hereditary It is, however, nearly always concordant in one-egg twins, but discordant in two-egg twins. Mongolian idiots hardly ever get offspring. The disease might therefore very well be conceived occasionally to arise by mutation and be hereditary, but never in-

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Various clinically specific forms of mental deficiency exist, of which the following will be mentioned.

Mongolian idiocy, or *mongolism*, is present in 0 02 to 0 03 per cent of the population and in about 0 15 per cent of new-born, almost equally often in boys and girls Nearly all the signs of Mongolian idiocy indicate retarded development The mortality rate is very high. Mongolism practically always occurs as solitary cases in the families. It has, indeed, sometimes been observed in siblings and other relatives of Mongolian idiots, but hardly more often than that it can be explained by chance sampling This affection is therefore believed to be non-hereditary. It is, however, nearly always concordant in one-egg twins, but discordant in two-egg twins. Mongolian idiots hardly ever get offspring The disease might therefore very well be conceived occasionally to arise by mutation and be hereditary, but never in-

herited, because the affected do not propagate. The mothers of Mongolian idiots are relatively old (an average of 37 years against 29 years for mothers of normal children). The incidence is less than 1 per 1000 births up to a maternal age of 30 to 34 years For the maternal age group of 35-39 years the incidence is 0.28 per cent, for 40-44 years 0.76 per cent and for 45-49 years 2.75 *per cent. The cause of mongolism is* as yet obscure. Even if a married couple has got one Mongolian child there is no need to advise against more children for eugenic reasons The morbid risk of mongolism or mental or neurological diseases is hardly increased at all for siblings or more distant relations of Mongolian idiots.

Tuberous sclerosis is much rarer than Mongolian idiocy. If localized in the brain it usually causes mental deficiency, but it may also have other sites. *It is often associated with adenoma sebaceum (Pringle's disease). It varies* considerably in degree and is inherited as an irregularly dominant disease (*vide* p. 265).

Amaurotic idiocy (*vide* p 257) is connected with a disturbance of the lipoid metabolism. We distinguish between an infantile and a juvenile form. Both forms appear to be recessive. Consanguinity of the parents is often seen

Phenylpyruvic oligophrenia or *phenylketonuria* was first observed in Norway by Folling 1934, and later found in many other countries, generally constituting 0.5 to 1 per cent of mental defectives in institutions, and about 0.002-0.004 per cent in the general population Most of the patients are idiots or imbeciles of a special type They have a urinary excretion of about 1 gram daily of phenylpyruvic acid ($C_6H_5CH_2$ COCOOH). The excretion is usually continous throughout life In the abnormals some enzyme able to dissimilate the laevo-phenylalanine is lacking According to Penrose, the disturbances of reflexes, resembling thyrotoxicosis, suggest an active poisoning of the organism by excess of abnormal metabolites The failure of pigmentation and impaired growth suggest an internal nutritional deficiency, and the low mental activity may be caused by diminished rate of oxydation

The disease is inherited as a rare recessive trait The frequency of consanguinity among the parents of the phenolketonuric is high, in the United States Institutions 5 per cent and in Norway 14 per cent were first cousins No abnormal character has been observed in heterozygous carriers.

Penrose emphasizes that the detection of carriers by means of closely linked marker genes might be a possibility in the future. The practical realisation of this possibility would, however, presuppose the existence of a medico-genetical registration through several generations. Such a registration could give information as to whether the two linked genes in a given family were present in the coupling or repulsion phase, (*vide* p. 50).

Microphthalmos and anophthalmos are frequently combined with oligophrenia (Sjögren and Larsson). The incidence of this combination has in Sweden been found to be 0.0012 per cent, responsible for 4 per cent of the cases of blindness of those who reach school age

The mode of inheritance is uncertain, perhaps sex-linked recessive; some cases are probably caused by exogenous factors.

Laurence-Moon-Biedl's syndrome characterized by mental impairment, pituitary dystrophy, retinitis pigmentosa, and polydactyly is recessive. The coincidence of so many symptoms may be due to linked or complementary genes Close relatives, who may be heterozygous carriers occasionally show some mild symptoms, e g obesity or polydactyly

Epilepsy and several types of malformations are common in mental defectives of all grades The skull is frequently deformed as in microcephaly and acrocephaly or cranial dysostosis

Cerebral diplegia or *symmetrical spastic paralysis* (*vide* p 274) is combined with mental deficiency in less than half of the cases. Some cases of this disease and other *cerebral palsies*, may be recessive. In these diseases there are instances of affected siblings, and parental consanguinity is reported to be more common than in the general population

SCHIZOPHRENIA The gene for schizophrenia, or dementia praecox, or juvenile insanity, is present in 0 7 to 0 9 per cent of the population The disease can probably be reckoned to manifest itself in a schizophrenic during one-third to one-quarter of his total life span, and to be present in its fully developed form in 0 2 to 0 3 per cent of the population More than half of the schizophrenics are patients in mental hospitals Family investigations have shown schizophrenia to be hereditary, a view which has been borne out by fairly numerous twin studies It has been difficult to procure unselected material and attain an indisputable result, but very comprehensive twin studies have shown a much greater concordance in one-egg twins (40 to 80 per cent) than in two-egg twins (5 to 15 per cent) In a small, very thoroughly investigated series of twins Essen-Moller did not find actual concordance in one-egg twins, but if one twin had schizophrenia the other nearly always presented a deviating personality or a definite psychosis

There is also some disagreement as to the mode of inheritance of schizophrenia Various facts suggest monomeric recessivity with a manifestation rate of 60 to 70 per cent, or possibly somewhat lower The possibility also exists, however, that schizophrenia should be regarded as irregularly dominant, among others because the disease is more frequent among the offspring of affected than among their siblings, and because consanguinity is not parti-

cularly frequent among the parents of schizophrenics. For the present we must therefore in the case of schizophrenia employ empirical figures, which are not particularly reliable either, having been collected by different workers under different conditions and on the basis of different definitions of the disease.

The morbid risk for children of schizophrenics is stated to be 16 per cent schizophrenics, and 33 per cent become what is called schizoid (psychopaths), i.e. individuals with particular personality traits and other mental peculiarities reminiscent of the signs and symptoms of schizophrenia. The latter one of the two percentage figures must, however, be accepted with some reservation, as the diagnosis of a schizoid personality may be difficult to make with certainty. But there is no doubt that a relatively great number of children of schizophrenics become mentally abnormal even if they do not acquire fully developed schizophrenia. If one parent is schizoid and the other schizophrenic the morbid risk for the offspring is considerably over 16 per cent. The risk is the greatest for the children of hebephrenics and catatonics, being 20 to 21 per cent, whereas it is only 10 to 11 per cent for those of paranoid schizophrenics. This is probably in some measure due to the fact that schizophrenia as a rule manifests itself at a relatively high age in paranoid schizophrenia. They therefore have a greater chance of getting normal conjugal partners than the hebephrenics and the catatonics, who fall ill at a young age.

If both parents are schizophrenic the morbid risk for the offspring is stated to be 60 to 70 per cent According to the results of recent investigations, this figure is, however, possibly somewhat too high For siblings of schizophrenics the morbid risk is 7 to 12 per cent. For grandchildren the morbid risk of schizophrenia is 2 to 5 per cent and of acquiring a schizoid personality 14 per cent For offspring of siblings the two corresponding figures are 1.5 to 4 per cent, and for cousins 2 and 10 per cent respectively. In the average population the figures are 0 7-0.9 per cent and 2.5 per cent All the stated figures concerning schizoid personalities are, of course, very uncertain

In schizophrenia genetic-hygienic measures are indicated to a certain extent, but perhaps less so than might *a priori* be expected This is in part because, as shown among others by Essen-Möller, the fertility of schizophrenics is reduced to under 50 per cent of the normal Many schizophrenics have, however, completed their family before the disease develops. Reduced fertility is also seen among the relatives of schizophrenics

Genetic-hygienic measures are indicated in cases of patients with unquestionable schizophrenia who live under such conditions that they have a chance of having offspring, e.g. a married patient discharged from hospital during a remission. This applies particularly if the other conjugal partner is

schizophrenic too, or schizothymic, or belongs to a family with a schizophrenic taint

If a schizophrenic woman has become pregnant induced abortion is indicated, not only for genetic-hygienic reasons, but also because the schizophrenic psychosis often is aggravated during pregnancy and the puerperium. Induced abortion is likewise justified if the father of the expected child is a schizophrenic, even if the mother is normal Where the taint is less pronounced general rules can hardly be made; but eugenic measures will here probably be indicated only in relatively few cases If people who themselves are normal, but who have relatives with schizophrenia, ask whether they may be justified in having children, there is generally no reason to advise them against it But if the families of both conjugal partners are severely tainted with schizophrenia, there may occasionally be reason to pronounce with greater reservation, and even in some cases definitely to advise against reproduction. Each case must, however, be assessed individually on the basis of the stated figures for the genetic prognosis

In case of a heterogenous taint, e g with schizophrenia and manic-depressive psychosis we must reckon with a summation of the morbid risk for the offspring Among close relations of schizophrenics we find increased susceptibility to tuberculosis Siblings of schizophrenics die about four times as often of tuberculosis as siblings of non-schizophrenics This relationship has been explained by the fact that the great majority of schizophrenics are of an asthenic constitution and that in both diseases there is a weakness of the reticulo-endothelial system (Kallmann)

No genetic relationship has been found between schizophrenia on one hand and psychopathy, mental deficiency, epilepsy, alcoholism, or criminality on the other Endocrine disturbances, e g hirsutism of masculine type, are often seen in schizophrenic females A study of relatives shows that the bearded condition is an independent constitutional derangement; there is no close correlation between endocrine disturbance and schizophrenia.

The entire group of schizophrenic diseases probably constitutes a genetic entity, the differences between the subgroups are hardly due to separate psychosis-producing genes The development of the disease, whether it occurs early or late, or runs a more or less deleterious course, depends on the external conditions of life In addition, however, constitutional type plays a definite part Thus, the majority and the most pronounced cases are found in individuals of the leptosomatic body type, whereas pyknics show greater resistance to this psychosis. Schizophrenic families frequently show a decline in social status from generation to generation.

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MANIC-DEPRESSIVE PSYCHOSIS. Manic-depressive psychosis most likely constitutes a genetic entity. Menopausal melancholia may not belong genetically together with true manic-depressive psychosis. Both family and twin studies have plainly shown that manic-depressive psychosis is hereditary. The exact incidence cannot, of course, be calculated of such a cyclic condition as this, where periods of illness are succeeded by more or less complete, sometimes long and sometimes transitory, symptom-free spaces of time, and where there is no sharp line of distinction from the normal. Modern workers set the morbid risk of manic-depressive psychosis in the population at 1.6 per cent, viz. 1.0 per cent for men and 2.2 per cent for women; previously it was estimated to about 0.4 per cent.

The disease is generally stated to be dominant. The manifestation rate has been set between 50 and 80 per cent. Strömgren regards 60 per cent for females and 20 per cent for males as a likely manifestation rate. Empirical figures are available for the different family groups. The morbid risk for manic-depressive offspring is about 25 per cent; but in addition about 15 per cent become mentally abnormal: emotionally unstable (cyclothymic) or with a permanent abnormal emotional level. If one parent is manic-depressive and the other cyclothymic, the corresponding figures are 30 and 18 per cent, and if both parents are manic-depressive, 40 and 50 per cent respectively In the latter cases a number of schizophrenics may often be seen among the offspring, possibly, however, because the manic-depressive psychosis of the parents was not quite pure. The morbid risk for siblings of manic-depressive is 10 to 15 per cent, for grandchildren 3 to 4 per cent, and for cousins as well as offspring of siblings 2 to 3 per cent One-egg twins show very considerable concordance with regard to manic-depressive psychosis. Multifactor inheritance cannot be excluded.

One and the same family may present marked variation with regard to the course and intensity of the disease; but some families show rather great *uniformity The manic-depressive genotype* shows a considerable range of phenotypic variability and is correlated to the genetic factors for gout, diabetes, and a tendency to obesity. Manic-depressive persons have a diminished chance of reproduction; their celibacy rates are increased and their fertility rates decreased.

A genetic prognosis can be made in conformity with the above figures; but we must also consider the fact that the disease, at least in its mild forms, cannot be regarded as severe and incurable As a rule it does not preclude development of *socially and individually valuable persons In the grave cases,* in particular those with a considerable hereditary taint, eugenic measures may, however, be indicated. But regarding this disease it is always necessary to act

by discretion in each individual case and be reserved with regard to taking such measures. Two manic-depressive persons marrying will probably in the general be advised against having children.

OTHER FORMS OF PSYCHOSIS The hereditary forms of *paranoia* are nowadays most often included under schizophrenia, and must therefore be supposed to show the same inheritance as this disease.

Senile psychosis and *involutional psychosis* are often hereditary, but the mode of transmission has not been elucidated It is stated that many of the patients who develop senile psychosis have been mentally abnormal all their lives. Senile psychopathy differs genetically from arteriosclerotic encephalopathy.

Compulsion neurosis and *anxiety neurosis* (including situation anxiety and claustrophobia) have been claimed to be related to the schizoid personality. It is doubtful whether we may be justified in doing so, but these forms of neurosis are at any rate occasionally seen to occur as familial traits.

There is not infrequently found a combined taint with different grave mental disturbances, without detailed information being procurable on the characters of these The data available may be rather vague, or the diagnoses may not have been based sufficiently on psychiatric evidence or not exact enough, e g. insanity, melancholia, nervousness, alcoholism, vagrancy, suicide, chronic unemployment, and other forms of asociality, or criminality. In such cases we cannot make an exact genetic prognosis, but the taint may be so unquestionable that it warrants eugenic measures being carried out (Fig 90).

DYSLEXIA, STUTTERING, AND LEFT-HANDEDNESS. The incidence of *dyslexia* in the normal population is judged to be about 10 per cent. The majority of the cases are hereditary and the inheritance is often dominant. Disturbances of speech, left-handedness, and other intellectual and mental defects may occur in the same families, a fact which argues in favour of regarding these conditions as genetic equivalents *Stuttering* is often a familial defect, which in some cases shows dominant inheritance. About half of the stutterers have relatives with the same defect of speech In these families there is, according to some statements, a certain tendency to epilepsy, hysteria, and mental deficiency as well A lisp, sigmatism, is also often a familial trait The same applies to audimutitas *Left-handedness* seems recessive It is more frequent in males than in females In one-egg twins it often occurs mirror-image-like, as previously stated Epilepsy and disturbances of speech are said to be particularly frequent among the left-handed Situs inversus viscerum is occasionally seen in siblings. Like left-handedness, it is possibly recessive. According to

Torgersen the developmental potentialities for bilateral differentiation of the human egg are so strongly determined genetically that the mirror-image mechanisme (*vide* p. 99) is of relatively small importance in human polyembryony.

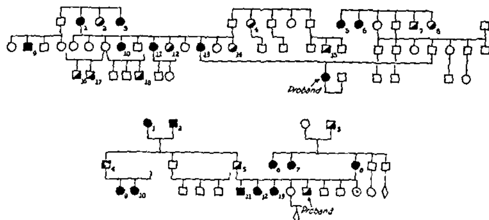


Fig. 90.—Instance of *combined taint* The proposita of the upper pedigree had been impregnated extramatrimonially by the propositus (proband) of the lower pedigree, and desired induced abortion at eugenic indication She presented no certain mental abnormality. But her mother (No 13 of the pedigree) was stated to suffer from mental depression. Besides, No. 1 of the upper pedigree had mental depression and attempted suicide, No 2 had had convulsive fits, No. 3 was eccentric, No 4 nervous, No 5 insane, No 6 insane, No. 7 chronic alcoholist, No 8 nervous, No. 9 schizophrenic, No 10 mental depression, No 11 insane, No 12 eccentric, No. 13 mental depression, No. 14 epilepsy?, No 15 comm suicide, No 16 habitual drunkard, asocial, No. 17 habitual drunkard, asocial, No 18 eccentric The father of the expected child, the propositus of the lower pedigree, was a tramp addicted to drinking His father was a habitual drunkard, his mother suffered from mental depression Besides, No 1 of the lower pedigree was asocial, No 2 tramp, No 3 habitual drunkard, asocial, No 4 nervous, No 6 mental depression, No. 7 unbalanced, No 9 schizophrenic, No 10 schizophrenic?, No 11 eccentric, No. 12 mental depression, No 13 asocial

Neurosis is a reaction between the personality and the environment; but genetical causes help to determine the susceptibility to influences producing neurosis.

Psychopathy. Psychopathy is due to a defect in the fields of emotion and will, which produces a psychic disharmony, has an unfortunate influence on character development, and reduces the power of adaptation Psychopathic personalities are characterized by emotional immaturity with marked defects of judgement and without evidence of learning by experience Special features are criminal traits, moral deficiency, vagabondage and sexual

perversion We can only roughly estimate whether mental disharmony is outside the range of normal variation, whether the individual under observation presents an "abnormal personality" so pronounced that it must be designated as psychopathy. But in some cases the individual is so severely affected or gives so much trouble to society that there can be no doubt that transmission of the disease to future generations must, if possible, be prevented.

Development of an "abnormal personality" depends to a great extent on external conditions In one environment mental disharmony can be subdued and the individual be regarded as mentally normal. In another environment the same psyche may develop in the opposite direction. Numerous environmental injuries may here accumulate over an originally rather small pathological nucleus, so that the individual concerned develops a grave psychopathy. Some cases of psychopathy are, however, so pronounced from the outset that they will manifest themselves in any environment. This group of psychopathies is of great interest from a genetic point of view.

According to the classical description psychopathy is constitutional and must be supposed to be hereditary. It does not manifest itself the first few years of life, often not till the age of puberty, or even later, when the individual concerned has to manage for himself

Psychopathy, or conditions indistinguishable from psychopathy, are rather often exclusively or chiefly of exogenous origin, e g. due to environmental influences, head injury, encephalitic processes, or the like. Such affections are, however, often designated as abnormalities of character.

Finally, a very considerable proportion of the psychopathies are of combined exogenous and endogenous origin. A certain, more or less pronounced "abnormal personality" develops, depending on the environment, into either a mild or a severe form of psychopathy. We do not know the exact incidence of psychopathy in the population. It is often set at 3 per cent, but the number of cases indicating genetic-hygienic measures is much smaller. The percentage number of psychopaths needing institutional care one way or the other has by some writers been set at 0 3. The most common types of psychopaths in men are the weak and impulsive, in women the asthenic, impulsive, sensitive and hysteric psychopaths.

Twin studies of true psychopaths show great concordance in one-egg psychopathic twins of the different types. Twin studies of criminals have given the *same result*, particularly among the habitual criminals, whereas no great concordance *has been* found among first time offenders. Juvenile offenders and problem children show very great concordance even in two-egg twins, a fact which *suggests* that the environment also has a considerable influence on the occurrence of this deviation from the normal

We should *a priori* expect it to be easy to find the empirical morbid risk figures for relatives of psychopaths in the different groups, but the material available is as yet too small to allow definite conclusions to be made. This is, of course, in some measure due to the difficulty of defining and classifying the group of psychopaths. A great number of family studies on relatives of criminals, pathological liars and swindlers, drug addicts, habitual drunkards, homosexuals, and true psychopaths are available, but only few of these were carried through by a fully satisfactory method from a genetic point of view.

An investigation starting from propositi with pronounced psychopathy, of whom 11.7 per cent had psychopathic conjugal partners and 32.5 per cent partners with strange traits of character, revealed a very high incidence of mentally abnormal persons among their offspring: 30 per cent were psychopaths, 43 per cent had strange traits of character, 2.4 per cent were mentally backward or deficient, and 2 per cent insane. 22 per cent of the male and 4 per cent of the female descendants had been punished. An investigation of habitual criminals showed that 37 per cent of their brothers, 28.4 per cent of their fathers, 17.5 per cent of their cousins, 11.2 per cent of their sisters, 14.3 per cent of their mothers, and 45 per cent of their wives were criminals.

If the mental condition of both parents is considered, the following figures have been recorded: Of the offspring of two psychopathic parents 85 per cent become mentally abnormal one way or the other. If one parent is a psychopath and the other shows slight mental deviation 74 per cent of the children become mentally abnormal, and if one parent is normal and the other a psychopath 70 per cent become mentally abnormal. These figures seem to argue in favour of dominant inheritance of psychopathy, but the conditions are so complex that we cannot be dogmatic on this question.

Certain forms of psychopathy are more or less markedly inherited as genetic entities. This is said to be the case particularly with the self-asserting type, including hysterical, mythomanic, and over-imaginative psychopaths, found in almost the same form in the offspring. The same applies, though less obviously so, to the depressive, weak, and vacillating psychopaths, as well as to the hyperthymic and the callous. However, only very few reliable observations are available concerning the hereditary conditions of the individual forms of psychopathy.

Habitual drunkards and *dipsomaniacs* are often psychopaths, especially nowadays. Many cases of alcoholism in a family are most often indicative of a psychopathic taint. Starting from drunkards as propositi we find among relatives a very great number of both drunkards and true psychopaths. Similar results are found if the propositi are *drug addicts*.

The above-mentioned twin studies of *criminals* convey, particularly where

habitual criminals are concerned, a strong impression that crime is dependent on hereditary factors One-egg twins display concordance not only as to whether they are criminals or not, but also with regard to the nature and severity of their crimes and to the number of their punishments, etc In the few cases of highly criminal one-egg twins showing discordance a natural explanation could be given of this, e g. that the criminal twin had had encephalitis in infancy

The idea of a relationship between a criminal disposition and hereditary factors is not new

It was strongly, certainly too strongly, expressed in the latter half of the 19th century, by Lombroso, for instance, who advanced the theory of the existence of criminal man, the born criminal characterized by physical and mental inherited traits *L'uomo* and *la donna delinquente* were alleged to proceed along their destined paths into criminality and prostitution. The degenerate families were thought to be marked by their mental and somatic signs of degeneration, including moral insanity and proper criminality, characterized by egocentric overrating, lack of social adaptation, or by direct antisocial thinking and conduct

There is no doubt a suggestion of truth in these old theories, although they contain misunderstandings and overshoot the mark in certain respects The characters predisposing to crime, like all other characters, develop by an interaction of gene and environment In some cases they are determined chiefly by environmental factors, while in others they may depend almost exclusively on hereditary factors, but most often they are due to a close interaction of both It then remains to be decided in each individual case whether heredity or environment play the greater part

The concept of criminality is not a fixed one. It is subject to ethical and social-legal estimations, which alter according to time and place. Criminality therefore cannot be regarded as a purely biological concept, and it by no means constitutes an aetiological entity Hence it is not expedient to study the inheritance of criminality as such We should rather attempt to find the causes of criminality and investigate which hereditary diseases and abnormalities are particularly frequent in criminals, and then determine the modes of transmission of these various nosologic entities

Within the past few decades numerous psychiatric investigations have been carried through on different groups of criminals The results achieved were in the main in agreement They showed that among criminals there are found many psychopaths, some mentally backward and mentally deficient individuals, and some psychotic

The number of defectives in a certain group of criminals depends, how-

ever, in a great measure on various external circumstances, e g. on the interpretation of the law, social conditions prevailing, the general standard education in the country concerned, and on whether psychiatric examinations of the criminals are made. In a Danish rural district Fremming in 1946 found the incidence of criminality to be 2 8 per cent for males between the ages of 15 and 55, and 0.6 per cent for females. According to G. Dahlberg (1943) the incidence of criminality in Sweden is 7 per cent for males living to the age of 70 and 0.8 per cent for females, twice as high in cities and towns as in rural districts Similar figures have been found in other countries.

Certain groups of crimes are often performed by mentally abnormal individuals, such as murder and homicide, incendiarism without an economic motive, sexual crimes, and first offences made by old persons. Nearly all habitual criminals are more or less abnormal The mental peculiarities most frequently seen in criminals are deficient development of the intellectual functions, and defects of character, including emotional hypoplasia. Psychopathy is the most pronounced feature in criminals, but true insanity may also occur. Schizophrenics, for instance, occasionally commit incomprehensible, cruel murders or crimes of violence, or they may, gradually as their personality becomes increasingly disorganized, take to begging and minor offences. Paranoics may now and then perform criminal acts in a state of fear of imaginary persecution, or they may commit the so-called crimes of conviction for political or religious reasons, which by some, perhaps not always without reason, are regarded as heroic deeds Melancholics not only commit suicide, but often also put the whole family or some of its members to death at the same time Maniacs may during their exalted periods perform any kind of violent acts. Epileptics are inclined to commit various crimes of violence, and mental defectives generally commit sexual crimes and crimes for the purpose of gain

In the so-called criminal and *asocial families* the worthless types develop by an interaction of unhappy environment and unfortunate hereditary factors, which are preserved and increased by negative selection

Many descriptions exist of anti- or asocial families Best known is probably the so-called Kallikak family (from Greek *kallos* = handsome and *kakos* = bad) described by Goddard. Among the members of the bad line of the Kallikak family there were numerous mental defectives, epileptics, habitual drunkards, criminals, prostitutes, tramps, etc., and the infant mortality was very high This line descended from a young man of respectable family who during the North American war of independence had a child with a mentally deficient woman After his return from the war he married a girl of good family. From this couple descends an able and respected family of great merits and high morality. The Juke family is another criminal family, in which there were found 366 beggars, 251 criminals and perpetrators of violence, and 10 murderers Further, there is the Nam family, whose most characteristic traits were mental defi-

ciency, alcoholism, and work-shyness In the Dack family many members were insane. In the Hill family epilepsy was a prominent feature. The Anable family was characterized by many drunkards and criminals, while in the Victoria family there were found particularly many illegitimate children

Several such asocial or directly antisocial families have been investigated and described in many different countries, among whose members were numerous criminals, tramps, habitual drunkards, mentally backwards, mental defectives, and psychopaths

An analysis of such families has revealed that anti- and asocial traits, to a considerable extent at any rate, are due to environmental influences, but that they also depend on the presence of hereditary factors

Furthermore, population groups who differ characteristically from the average by their mode of living, descent, or the like (*e.g.* gipsies, prostitutes, alcoholists and groups of individuals displaying asocial conduct), have been submitted to comprehensive genealogical, social-biological or psychiatric studies

Experience from such investigations has shown that a thorough biological knowledge of the population and its individual groups is a necessary basis for an adequate social and population policy

Part V

GENETIC HYGIENE

Chapter 31

FROM EUGENICS TO GENETIC HYGIENE

Quantitative and Qualitative Eugenics. Francis Galton, who in 1883 introduced the science of eugenics, defined it as follows, "Eugenics is the science which deals with all influences that improve the inborn qualities of a race, also with those that develop them to the utmost advantage".

A distinction was subsequently made between quantitative and qualitative eugenics. *Quantitative* eugenics deals with the too rapidly as well as the too slowly increasing, or positively decreasing growth of a population Population statistics seems to show that when a civilized nation has reached a certain stage of development the growth of the population begins to decrease. The mortality rate falls, indeed, with increasing civilisation, but the birth rate falls markedly, too The excess of births will decrease steadily, finally to be changed into a deficit of births Attempts have been made to check this development by various practical measures These having, however, been based on political rather than on scientific views they will not be described here. Yet there may be reason to mention that such measures have been attempted as improved housing for families with many children, establishment of day nurseries in slum quarters, introduction of tax modifications and financial benefits in proportion to the number of children There is no evidence to suggest that such measures will lead to overpopulation, as occurs on the contrary in underdeveloped communities

Qualitative eugenics deals with the quality and not with the quantity of the population We distinguish here between positive and negative eugenic measures.

Positive and Negative Eugenics *Positive* eugenics meets with almost insuperable difficulties. Superman cannot be artificially produced Marriage and reproduction cannot be carried through by compulsion Indirectly posi-

the eugenic purposes have been pursued, and perhaps not unsuccessfully, but we cannot with certainty characterize the ends gained this way as an advantage to humanity Accordingly no detailed account will be given of positive eugenics either.

Negative eugenics arose nearly 70 years ago in connection with the great progress made in natural science by the end of the 19th century, with a direct bearing on Darwin's theory of evolution and as a consequence of this.

However, by the time the concept of eugenics was formed the conditions for its practical employment were not yet present Nearly 50 years elapsed before medical genetics, in connection with the introduction of modern biological genetics, had reached such a development that it could form a basis for eugenic measures being carried out.

The correct use of eugenics was not recognized for the first 50 years after its introduction

From the outset it was associated with an idea that particularly valuable families exist whose propagation ought to be encouraged. These ideas, marked by the English thought of "the fit contra the unfit" and of "the good human stocks" were rather obscure, though in the main harmless In America, on the other hand, the first development of eugenics was associated with an idea of the existence of particularly harmful and dangerous families, who are very expensive to society. The aim of eugenics therefore here became that of sparing society this expense

In Germany eugenics underwent a more disastrous development with its unrealistic ideas of superman and worthless racial elements, a development which ended in a catastrophe

To our knowledge eugenics has not yet obtained a footing in Eastern Europe, because the development that has taken place here during the past few decades within the biological sciences differs somewhat from that in Western Europe The basis for an understanding of genetic hygiene is therefore not yet present in these countries.

Genetic Hygiene. In the Scandinavian countries various eugenic provisions have been introduced during the past 20 years These are chiefly based on the view that eugenics is a purely medical subject with the sole task of preventing disease This form of eugenics is termed *genetic hygiene*.

Genetic hygiene corresponds in the main to the negative qualitative eugenics, and may, besides, be characterized as follows:

It rests definitely on the principle of voluntariness Genetic-hygienic measures are taken exclusively at the desire of the persons concerned Experience shows that patients, after having been informed on the significance of the

hereditary taint, nearly always follow their doctor's advice within this field. Compulsory measures are never employed within genetic hygiene.

In the countries where genetic-hygienic laws exist containing directions for the employment of eugenic measures, these laws guide patients and doctors, and they contain securities against the misuse of the often serious measures which have to be taken.

GENETIC-HYGIENIC MEASURES. The most important negative eugenic measures are sterilisation, induced abortion, prohibition of marriage, matrimonial advice, combined with instruction on contraception, and other forms of genetic advice, and finally segregation of the individual in a hospital or other institution. Sterilisation and induced abortion will be mentioned in the following chapter.

The laws dealing with genetic-hygienic control of marriage differ considerably in various countries

In some countries special clinics have been established for the purpose of giving matrimonial advice Information on contraception is usually given here at the same time In Denmark matrimonial advice is frequently given by general practitioners as well as by specialists. The possibilities within this field will gradually increase with increasing medical research within heredity. Genetic counseling will in future become a comprehensive and important medical task

It is also a matter of genetic-hygienic importance that patients with hereditary diseases should stay for a considerable length of time in hospitals or institutions, or be kept under public care. This results in a shorter or longer segregation of such individuals, which naturally lowers their changes of propagation. Thus, hospital or institutional treatment, public care, and general knowledge of the mental defectives, epileptics, deaf, blind, and crippled are of genetic-hygienic importance

Finally, the break-up of isolates where inbreeding causes recessive diseases to prevail, may be of genetic-hygienic significance If such inbred groups are scattered throughout the population, as happens relatively often nowadays owing to improved communications, their respective hereditary diseases will cease to appear. On the other hand, the taint will become more widespread, and this may in the course of time involve a certain risk

It is sometimes stated that the main purpose of genetic hygiene is to spare the community a great deal of expense This is, of course, a great mistake. Negative eugenic measures are of an entirely medical character aiming at preventing disease and misfortune Like other preventive measures within medicine they naturally mean a saving to the public in the long run, as

the diseases would have cost far more than the amount expended on their prevention

THE BASIS OF GENETIC HYGIENE. Genetic hygiene as defined here is of recent date The basis for a correct execution of genetic-hygienic measures has only existed during the past few decades

In the first instance there is reason to mention the great development which medical genetics has undergone and the extensive knowledge of its results, not only among physicians, but also to some extent in the general population A thorough instruction of human genetics, especially genetic pathology, ought therefore to be included in the medical curriculum. Furthermore, general information on the spread and significance of the hereditary diseases constitutes a basis for genetic hygiene

Other requirements must also be fulfilled before an efficient genetic hygiene programme can be carried through. The public health system and social care must be well-organized Where hospitals and other institutions for diseased and defective individuals, as well as the public care system have attained a certain standard, we can through these institutions trace many patients with hereditary diseases These patients will then be isolated or be under some control during the period of their reproductive power On the other hand, the carrying through of efficient social laws presupposes genetic-hygienic measures

Moreover, a medico-genetic registration carried through in the various countries or parts of countries would be a great aid for the correct effectuation of genetic hygiene

By such a *genetic-hygienic registration* we understand elaboration, as far as possible, of a complete register or card-index, continually brought up to date, of all the patients with severe hereditary diseases within a certain area, and of their family members

A registration of this kind can in many ways be of aid in genetic-hygienic questions In the individual cases the data of the patients concerned and their relatives can easily be procured and used as a basis for a solution of the genetic-hygienic [illegible]

hygienic [illegible]

in a pop[illegible] they decrease or increase in frequency and form an estimate as to whether the genetic-hygienic measures are carried through in the right way in the cases of diseases where it is an advantage to make use of these measures, and only in these cases Finally, a genetic-hygienic registration may *constitute* a starting point for medio-genetic studies, which, as previously mentioned, form the necessary basis for all genetic-hygienic activity

Chapter 32

GENETIC-HYGIENIC LAWS

The genetic-hygienic laws introduced during the past 50 years or so in various countries indicate how genetic-hygienic views have come to prevail in a steadily increasing number of places. They show how the first faltering attempts have been made to solve the genetic-hygienic problems, and will therefore here be briefly mentioned

The genetic-hygienic laws employed so far fall within the following domains: sterilisation, induced abortion, marriage and social laws

Sterilisation. The first sterilisation for eugenic purposes is generally stated to have been performed in 1899 by Harry Sharp, prison medical officer at Jeffersonville in the State of Indiana, U S.A

Males are generally sterilized by vasectomy X-ray sterilisation and hormonal sterilisation have been tried, but these procedures have the disadvantage, among others, that it is difficult to obtain absolute sterilisation without at the same time producing symptoms of castration. They are therefore comparatively rarely employed.

In females sterilisation is usually performed by salpingectomy X-rays have also been employed for sterilisation of females, but it is difficult to give a sufficiently large dose to obtain a definite sterilizing effect without at the same time producing castration-like symptoms Their use is accordingly limited to women approaching the menopausal age

Attempts have been made within recent years to refertilize, by surgical intervention, sterilized men or women who desire to become fertile again Such re-operations are rarely successful, however

Sterilisation is not followed by disability symptoms similar to those seen after castration Sterilisation on the whole causes only very little inconvenience The sexual life of the patient continues to be normal after the operation Women may have a transitory period of irregular menstruation immediately after the operation There is no evidence to suggest that sterilisation should lead to unchecked sexual intercourse or involve a risk of increased spread of venereal diseases The sterilized often obtains a resocialisation in consequence of the operation It has been stated by a single writer that females especially may develop neuroses or depressive states following sterilisation, but these do not seem to be of a serious nature, and are on the whole relatively rare

The operation risk in cases of sterilisation is low, in males almost *nil*. In females, where the operation is that of laparotomy, a certain limited risk is, of course, involved Von Hofsten' (1949) calculated the mortality risk for physically normal women submitted to sterilisation at about 0 1 per cent.

In 1907 the State of Indiana, U S.A, enacted the first sterilisation bill. In 1909 similar bills were enacted in California, Washington, and Connecticut. Before 1920 the same had been done in 18 States, before 1930 in 25, and before 1940 in 30, to which was later added the island of Puerto Rico.

It is difficult to make a survey of the contents of the many different sterilisation laws employed in the U.S.A. during the first few decades after 1907. They underwent many changes, and a number were rejected as "unconstitutional". It seems as if some of them at periods were used very little or not at all. The decisions as to who ought to be sterilized were based on different principles.

Mental deficiency indicates sterilisation in all the 30 States mentioned, mental diseases in all except one, and epilepsy in all except 7, further, in a few States also nervous diseases, physical malformations, and general hereditary conditions. Finally, in 9 States habitual criminals may be sterilized, and in 9, in part the same, serious sex-delinquents.

In many of the States compulsory sterilisation is permitted under certain circumstances.

In the U.S.A. over 50,000 sterilisations were notified 1907-1948 in the 30 States having sterilisation laws. Two-fifths of the sterilized were males. Mental deficiency was the most frequent indication; but mental diseases followed very close. During the 41 years there were only 3,000 cases having other causes. About two-fifths of the sterilisations were performed in *California*, the State with the relatively greatest number of these operations.

It is difficult to assess the effects of the sterilisation laws in the United States, where the conditions vary from State to State and where the individual laws have changed in the course of years. In several States where sterilisation previously was rather extensively used this operation has obviously later been abandoned. On the whole we may probably say that the sterilisation laws and their application in the U.S.A. have not yet been finally established. They have not always rested sufficiently on a medico-genetic basis, nor have they always been based unconditionally on the principle of voluntariness.

Sterilisation laws also exist in various countries outside the U.S.A. and Europe, e.g. in several Canadian provinces, in Alberta since 1928, and in British Columbia since 1933. In Tasmania and New Zealand proposals of sterilisation laws have been put forward.

In *Europe* sterilisation laws have existed since 1929. They were first introduced in the Canton of Waadt in Switzerland, and later in same year in Denmark. Then followed Norway (1934), Sweden (1935, revised 1941), Finland (1935), and Iceland (1938). In Germany (from 1934) and Esthonia they have had sterilisation laws which probably are no longer in force. In other countries, such as England, Holland, Hungary, Czecho-Slovakia, and Poland, sterilisation laws have been considered, but not carried through.

In 1951 sterilisation laws are thus found in all the Scandinavian countries

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of 15 years. If sterilisation was performed to a similar extent in the U.S.A., this would mean about 47,000 sterilisations a year.

A number of the above sterilisation laws also contain provisions concerning castration. Legal castration cannot be regarded as a genetic-hygienic operation. It is performed chiefly for criminal-therapeutic and social reasons. No account will therefore be given of castration in this book.

TABLE 23.

Total number of legal sterilisations and abortions in Denmark (1945: 4,045,000 inhab.) 1929-1950

	Sterilisations males	Sterilisations females	Sterilisations total	Abortions
1929-34	20	88	108	—
1935-39	405	975	1,380	—
1940-45	610	1,510	2,120	5,705
1946-50	561	1,771	2,332	13,801
Total, 1929-50	1,596	4,344	5,940	(1940-50): 19,506

INDUCED ABORTION. Nearly 2,300 years ago Platon mentioned the possibility of induced abortion for eugenic reasons. His proposal passed unnoticed, however. In 1939 Denmark, Iceland, and Sweden introduced laws permitting induced abortion on eugenic grounds. In 1950 similar laws were introduced in Finland.

According to the Danish Abortion Act induced abortion may be complied with if desired by the pregnant woman, and if there is an obvious risk of the child being liable to inherit insanity, mental deficiency, other grave mental disturbances, epilepsy, or severe and incurable physical diseases.

Whether the conditions mentioned in this Act are present in each individual case must be decided by the physicians concerned, i.e. the general practitioner of the woman in question or the physician attached to a Maternity Welfare Institution, in consultation with another authorized physician, often the chief of the surgical or gynaecological department where the operation is to be performed. It is often necessary first to refer the woman to some specialist or to have her admitted to a psychiatric or other non-surgical department.

Abortion normally must be induced only within the first 3 months of pregnancy (in Sweden within the first 20 weeks).

As appears from Tables 23 and 24, the number of legal induced abortions have increased considerably year by year. A large proportion of the operations have been performed entirely or in part on eugenic grounds. In Denmark

The first Danish Sterilisation Bill was enacted in 1929, revised in 1935. According to this Act a person who applies may be sterilized if sterilisation is indicated for social reasons; furthermore (1), in the cases of mentally normal individuals, if there are particular indications, especially a risk that a predisposition may be inherited by the offspring; and (2), where mentally abnormal individuals are concerned, who are not true mental defectives, if it is regarded to be to the benefit of the person concerned that he (or she) is made unable to produce offspring The application for sterilisation, directed to the Department of Justice, must, among other things, be accompanied by a medical certificate giving adequate reasons for sterilisation The Department of Justice must in each case consult the Medico-Legal Council.

Mental defectives may be sterilized if there are social (including genetic-hygienic) reasons against their having offspring, e g if they are judged to be so defective as to be incapable of adequately providing for or educating their children Application for sterilisation is directed to the Department of Social Affairs. Permission must in each case be rendered by a special board comprising a judge from the Supreme Court as chairman, a psychiatrist, and a person experienced in sociology. In doubtful cases the Director of the University Institute for Human Genetics is consulted

There is reason to point out that the patient himself must apply for sterilisation, this being, in other words, voluntary, and that each case is thoroughly tested and assessed by medical experts. In the other Scandinavian countries sterilisation laws follow in the main the same principles, though differences are found

The total number of sterilisations was in Denmark for the first 21-22 years about 6,000, as Table 23 shows. During the next 20 years it will probably exceed 10,000.

Just over two-thirds of the individuals submitted to sterilisation were mental defectives, and of these, about two-thirds were females Among those sterilized for other indications than mental deficiency the preponderance of females was even higher, about seven-eighths Of late years almost equally many mentally deficient and individual without amentia have been sterilized. In 1950 the latter for the first time exceeded the former in number. Various other hereditary diseases, besides mental deficiency, warranted sterilisation, e.g. *mental diseases, psychopathy, nervous diseases, diseases of internal organs*, eye and ear diseases, skin diseases, and malformations In no small number of cases there was a supporting medico-social indication

According to a statement by von Hofsten in 1949, the number of sterilisations in Sweden from 1935 to 1948 amounted to about 15,650. Of these, 12,700 were performed within the period July 1, 1941 to December 31, 1948 Hofsten states further that in 1948 alone the number of sterilisations was about 2,200, i e. more than 0 03 per cent of the total population and corresponding to 1.8 per cent of the number of children born who reach the age

is, however, absolutely necessary that the physician takes the, sometimes very great, trouble of procuring information on the family. In Denmark the genetic-hygienic register at the University Institute for Human Genetics, Copenhagen, may be of aid for such an investigation.

The initiative towards the employment of genetic-hygienic measures may come from different parts. Application may be made to the physician by the

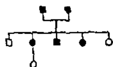


Fig 91.—Mental deficiency Instance 1

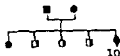


Fig 92.—Mental deficiency Instance 2.

patient himself, his near relations, the social committee, or by others. The initiative may, however, also very well come from the physician.

The genetic-hygienic problems confronting the general practitioner will be exemplified below

Mental deficiency is no doubt the affection which most often indicates genetic-hygienic measures being carried out Many different and difficult eugenic problems may arise here, as may be illustrated by the following instances

1. A *feeble-minded* married couple has 5 adult children The eldest is a man of normal intellect and the youngest a girl likewise of normal intellect, while the 3 others are feeble-minded The *eldest* wants to marry and asks whether there is indication for sterilisation As mentioned above, we must, when asked such questions, procure the most exact family data *possible* In the present instance there proved to be no hereditary taint in the family of the fiancée, and as the man himself also was normal, marriage and reproduction cannot be advised against.

The eldest daughter is 32 years old, quiet and able to work, mildly feeble-minded, 15 years ago she bore an *illegitimate* child of normal intellect She stays with her mother and a feeble-minded brother The local social committee raises the question whether it is necessary to place her under care for mental defectives and have her sterilized As she has displayed no particular sexual desire since the birth of her first child, sterilisation does not seem to be required, but she ought to be under the supervision of the Mental Deficiency Authorities

The youngest daughter, who is normal, is 2 months pregnant The father of the expected child is unknown She now desires abortion induced There is, however, no absolute genetic-hygienic indication for induced abortion, as the morbid risk for the offspring of siblings of mental defectives is only about 10 per cent.

2 A *feeble-minded* couple has 14 children of whom 11 are mentally *deficient* and 3 mentally backward. The *eldest*, a woman, aged 26, is mildly feeble-minded She stays

probably 500 to 1,000 abortions annually are induced mainly for eugenic reasons.

GENETIC-HYGIENIC ADVICE. The task of the physician in connection with the genetic-hygienic laws is in the first instance to make a genetic prognosis for the offspring of a person or a married couple in cases where information is available on diseases in one or both parents and in their families. It is by no means always possible to indicate a definite percentage figure for the chance that a child in whose family a certain hereditary disease occurs will inherit the disease Where advice is to be given one's estimate of the risk will in some measure be influenced by the severity of the disease concerned. In cases of particularly severe and deleterious diseases we are inclined to take consideration of even rather low percentage figures for the chance of inheritance Furthermore, the case is very often complicated by other considerations, e.g the fact that the patient cannot provide for and educate possible children. Induced abortion may be greatly desired by the pregnant woman, and the eugenic reasons may be supplemented by medical or social indications

TABLE 24.

Legal abortions and sterilisations in Sweden (1946 · 6,764,000 inhab) 1943-1948. (From v. Hofsten and Statistique officielle de la Suède).

	Sterilisations males	Sterilisations females	Sterilisations total	Abortions
1943	458	869	1,327	703
1944	588	1,103	1,691	1,088
1945	465	1,282	1,747	1,623
1946	—	—	1,847	2,378
1947	286	1,834	2,120	3,534
1948	—	—	2,278	4,585

In the case of matrimonial advice the physician is faced with similar problems as those which confront him in the employment of genetic-hygienic laws. He is asked about the advisability of having children by patients with some hereditary taint or other These questions may often be difficult to answer

A physician who is to make a genetic prognosis must, of course, know from which hereditary diseases the parents suffer But, in addition, he must, as far as possible, procure information on the hereditary taint in the families Not all physicians have realized this fact For a proper genetic prognosis it

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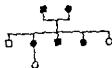


Fig 91.—Mental deficiency Instance 1.

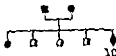


Fig 92.—Mental deficiency. Instance 2

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The youngest daughter, who is normal, is 2 months pregnant. The father of the expected child is unknown. She now desires abortion induced. There is, however, no absolute genetic-hygienic indication for *induced* abortion, as the *morbid* risk for the offspring of siblings of mental defectives is only *about* 10 per cent.

2 A *feeble-minded couple* has 14 children of whom *11* are mentally deficient and 3 mentally backward. The eldest, a woman, aged 26, is mildly feeble-minded. She stays

with her parents, where she can do light housework. She is 2 months pregnant The father, an unmarried labourer of normal intellect, wants to marry her. *Her parents* ask whether there is a possibility of induced abortion As, however, this is against the desire of the woman herself, it cannot be carried through But she may, perhaps, be persuaded to both induced abortion and sterilisation. In several countries the laws forbid her to marry unless she consents to sterilisation

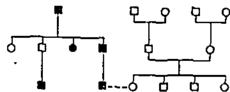


FIG. 93 —Psychopathy (chronic alcoholism suicide, criminality, asociality) Instance 3

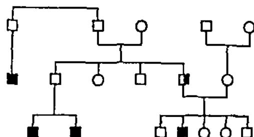


FIG 94 —Psychopathy and mental deficiency Instance 4.

Although little is known as yet of heredity in psychopathy and the diagnosis often is difficult to establish, we not infrequently meet with situations in which there can be no doubt about the justification of genetic-hygienic measures, as appears from the following instances

3. A normal woman, aged 21, of a healthy family is with child by a labourer, aged 28, who has 4 times been a patient in a mental hospital, has received a conditional condemnation for theft, and has been prosecuted for outrage of public decency He has been under psychiatric observation, from which the following information is available Diagnosis *Constitutional psychopathy*, sluggish, wanting backbone and energy, impulsive, affectible, void of buoyancy, emotionally unstable, repeated attempts at suicide, *homosexual, chronically unemployed. His father and his paternal grandfather* are habitual drunkards, the latter committed suicide A child of a sibling of his father committed suicide, and one of his own siblings is very nervous The woman now applies to her doctor to ask whether abortion can be induced

Before answering this question the physician must first procure the above data, if they are not already available, and, of course, ensure, as far as possible, that they are correct If the physician cannot himself procure the stated information, he must seek assistance *elsewhere He may then often collaborate to advantage with the Maternity* Welfare Institution. Next he must consult another physician, as a rule one attached to a hospital, or a specialist within another branch Their decision in a case like the one here reported depends, of course, on individual judgment, but the majority will probably decide on induced abortion, in countries where it is lawful

4. A 34-year-old normal pregnant woman of a *healthy family* is married *with an asocial* man, presumably a *psychopath*, in whose family there are 2 mentally deficient *brother's children* and a mentally deficient male cousin. The married couple have 5 chil-

dren One suffers from congenital *mental deficiency*. The others, who are all under age, are of normal intellect, as far as can be gathered The woman applies for induced abortion, and her request is complied with, because one of her children probably suffers from hereditary mental deficiency, and the morbid risk for siblings of mental defectives is 13 to 18 per cent. But the surgeon raises the question of sterilisation in connection with the induced abortion If the woman herself desires it, her desire can be complied

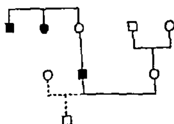


Fig 95—Psychopathy, alcoholism, criminality. Instance 5



Fig. 96—Manic-depressive insanity. Instance 6

with, if permission is given by the Department of Justice. It would be more reasonable and a smaller operation to sterilize the husband, but the male partners are known by experience to consent very rarely to sterilisation

5 A normal woman, aged 22, of a healthy family is 2 months pregnant by a man, aged 26, who since infancy has displayed *psychopathic traits*, and after he grew up has been *punished* several times for larceny, fraud, and swindling, by imprisonment in a juvenile prison and a prison for psychopaths. On the whole he has proved inconstant and unreliable, has continually changed occupations 5 years ago he [illegible] another wom[illegible] cured concer[illegible] was a habit[illegible] psychopathic traits. As there is no doubt that the father of the expected child suffers from pronounced constitutional psychopathy, there must be judged to be an obvious risk that the child will suffer from severe hereditary mental disturbances Hence there is eugenic indication for induced abortion Sterilisation of her husband is unquestionably likewise indicated, but this can, of course, only be carried through with his own consent.

In cases of mental diseases genetic-hygienic questions do not arise so often in general practice as might have been expected, at least not the questions whether sterilisation or induced abortion are indicated. But in such cases eugenic advice is not infrequently needed.

6 A man, aged 30, has twice been ill with typical *manic-depressive insanity*. Each time he stayed in hospital for about one year His last stay was 2 years ago His father and his paternal grandmother have also had a manic-depressive mental disease. He now intends to marry a normal woman of a healthy family and asks whether it is inadvisable to get children The answer must be that the chance of his children getting

with her parents, where she can do light housework. She is 2 months pregnant. The father, an unmarried labourer of normal intellect, wants to marry her. Her parents ask whether there is a possibility of induced abortion. As, however, this is against the desire of the woman herself, it cannot be carried through. But she may, perhaps, be persuaded to both induced abortion and sterilisation. In several countries the laws forbid her to marry unless she consents to sterilisation.

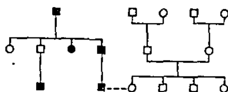


Fig 93—Psychopathy (chronic alcoholism suicide, criminality, asociality) Instance 3

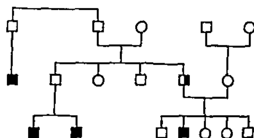


Fig 94—Psychopathy and mental deficiency. Instance 4

Although little is known as yet of heredity in psychopathy and the diagnosis often is difficult to establish, we not infrequently meet with situations in which there can be no doubt about the justification of genetic-hygienic measures, as appears from the following instances.

3 A normal woman, aged 21, of a healthy family is with child by a labourer, aged 28, who has 4 times been a patient in a mental hospital, has received a conditional condemnation for theft, and has been prosecuted for outrage of public decency He has been under psychiatric observation, from which the following information is available Diagnosis. *Constitutional psychopathy*, sluggish, wanting backbone and energy, impulsive, affectible, void of buoyancy, emotionally unstable, repeated attempts at suicide, homosexual, chronically unemployed His father and his paternal grandfather are habitual drunkards, the latter committed suicide A child of a sibling of his father committed suicide, and one of his own siblings is very nervous The woman now applies to her doctor to ask whether abortion can be induced

Before answering this question the physician must first procure the above data, if they are not already available, and, of course, ensure, as far as possible, that they are correct. If the physician cannot himself procure the stated information, he must seek assistance elsewhere. He may then often collaborate to advantage with the Maternity Welfare Institution Next he must consult another physician, as a rule one attached to a hospital, or a specialist within another branch Their decision in a case like the one here reported depends, of course, on individual judgment, but the majority will probably decide on induced abortion, in countries where it is lawful

4 A 34-year-old normal pregnant woman of a healthy family is married with an *asocial* man, presumably a *psychopath*, in whose family there are 2 mentally deficient brother's children and a mentally deficient male cousin The married couple have 5 chil-

Child Guidance Authorities The father of the child is liable to punishment, but genetic-hygienic measures are hardly warranted

10 A married woman, aged 42, is normal and of a healthy family. Her husband has for many years been suffering from typical progressive muscular dystrophy affecting the lower extremities and receives disablement benefit. He has 4 brothers and 6 sisters 2 of the 4 brothers suffer from muscular dystrophy The married couple have 1 daughter and 2 sons The youngest son, aged 11, displays mild signs of muscular dystrophy. The father also has a nephew with muscular dystrophy. The disease having been inherited from father to son it cannot be the recessive sex-linked form manifesting itself particularly in males In this family the disease occurs in childhood and has a disabling effect Induced abortion is therefore indicated in the present case. Sterilisation need hardly to be considered owing to the patient's age.

If genetic-hygienic questions are raised in connection with cases of blindness, deaf-mutism, or other severe ear and eye diseases, it is, of course, necessary first to ascertain whether these cases present the hereditary forms of the affections. If so, they are of eugenic interest.

11 A woman, aged 35, of a healthy family suffers from *aniridia*. She has 5 children, of whom 3 have aniridia. Her husband and all his relatives are normal, more *particularly* no eye diseases occur in this family. We know that aniridia is dominant and probably often occurs by mutation. Hence there is reason to suppose that half of the patient's children will get aniridia, which is a severe disease causing considerable impairment of vision The patient has become pregnant again and desires induced abortion and sterilisation. Both are indicated

12 Two deaf-mutes intend to marry. Examination of their families revealed that they both suffer from sporadic recessive *deaf-mutism* The Marriage Act does not forbid them to marry, and it is for themselves to decide whether they want sterilisation of one partner. If, however, a physician is familiar with the actual conditions, he ought to advise them against having children, as these will probably all become deaf-mute.

13 Here we have *a normal* man whose mother suffers from acquired deaf-mutism, while his father probably suffers from hereditary deaf-mutism(the sporadic recessive form). A father's brother is likewise deaf-mute The man wants to marry a normal woman with no hereditary predisposition to deaf-mutism [illegible]

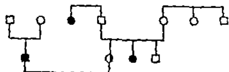
[illegible] couple against having children

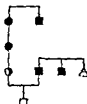
Numerous physical malformations may, of course, also indicate genetic-hygienic measures, as the following instances show.

14 A married couple has had 2 children who both died in early infancy from spina bifida aperta Both parents have spina bifida occulta, which has never troubled them A nephew of the father's died in early infancy from spina bifida Several other nephews suffer from nocturnal enuresis. Now they ask whether they dare have more children It is difficult to give advice in this case, because the inheritance of spina bifida is not yet fully clarified But it must at any rate be pointed out to the married couple that the risk of having another affected child is rather considerable.

the same disease as himself is relatively high, about 25 per cent, but that, on the other hand, it is a disease which may be relatively benign and be of fairly short duration

7. A man, aged 32, to all appearance of a healthy family, suffers from *schizophrenia* and has for 4 years been a patient in a mental hospital. His wife is of a somewhat sullen disposition, and she has a sister and a father's sister who both suffer from schizophrenia The man is discharged during a remission after shock treatment and moves to his home,


Fig 97.—Schizophrenia Instance 7


Fig 98—Epilepsy. Instance 8

where he is attended to by his physician. If the patient himself does not realize that he ought not to get more children, the physician must tell him, and possibly help him to have sterilisation carried out, in case he wants it

Several nervous diseases are of genetic-hygienic interest, thus in some instances epilepsy, but also Huntington's chorea (*vide* Fig 84, p 273) muscular dystrophy, and many rarer neurological diseases

8. A married woman, aged 30, who is 2 months pregnant, has since childhood suffered from petit mal The electroencephalogram shows dysrythmia having the characteristic spike-and-wave formation Her mother had *epileptic fits* between the ages of 14 and 35 The maternal grandmother and the brother of the latter suffered from epilepsy The patient's husband has during the past 12 years regularly had epileptic fits (EEG shows dysrythmia), and 1 of his 8 siblings is epileptic Several years ago the patient bore a child who is still healthy She now applies for induced abortion and sterilisation The fact that hereditary epilepsy occurs in the families of both conjugal partners is sufficient eugenic indication for induced abortion and sterilisation

9. A girl, aged 13, has during her childhood been suffering from typical epileptic fits of unknown cause She has been hospitalized twice for this disease Her paternal grandfather was a dipsomaniac, her mother's paternal grandmother was epileptic, and her mother's male cousin was of weak intellect, a psychopath, excitable, a habitual drunkard. She is 5 months pregnant The father of the expected child is a healthy 19-year-old apprentice smith. His father was addicted to drinking and punished 12 times. Three of his father's brothers have been punished 4, 3, and 18 times respectively for larceny, fraud, rape, obscenity, intoxication, etc His paternal grandfather was a habitual drunkard.

As the patient herself is under age and epileptic and the father of the expected child has an epileptic taint, induced abortion is indicated, but this cannot be carried through, because *the gestation period is well over 3 months* Heart sounds have been heard and life been felt The patient therefore has to be submitted to the care of the

eugenic indication for induced abortion. As she is intelligent, and familiar with methods for birth control there is no reason for sterilisation.

It appears from the above instances that the general practitioner often meets with genetic-hygienic problems which may be difficult to solve on the basis of our present knowledge. The possibilities of improvements in this respect will be discussed in the final chapter.

Chapter 33

FUTURE DEVELOPMENT OF GENETIC HYGIENE

Genetic hygiene can, as stated, be rather extensively used in practice; but this is attended by numerous difficulties and problems.

Experience shows that the patients themselves as well as their relatives nearly always realize the expediency of genetic-hygienic measures and therefore want to co-operate. Still, it is obvious that measures which interfere so radically with the fate and most intimate life of the human individual may arouse some friction or conflict of views. The physicians and other authorities dealing with eugenic cases ought always to be most considerate and thorough in their investigations, and the principle followed is always that too few genetic-hygienic operations are preferable to too many.

An important aid to the carrying through of eugenic measures is the establishment of a *genetic-hygienic registration* comprising a register or card-index covering all the patients in the country who are afflicted with a serious hereditary affection, and also their families. Such registers have been made in small districts in various countries. In Denmark, however, a genetic-hygienic register of this kind exists covering the whole country. This register, probably the first to comprise a whole country, was started in 1938 and is kept at the University Institute for Human Genetics, Copenhagen. Here it is tried, as far as possible, to procure information on all the persons suffering from any serious hereditary disease or defect, and on their families, too. If in a given case the question of genetic-hygienic measures is raised, the card-index may furnish information about the person or persons in question and their families. It will thereby in many cases be much easier to give an advice.

It is impossible to predict with certainty the results attainable by negative eugenic measures. They can never lead to complete eradication of inherited

15. A married woman, aged 36, suffers from *multiple cartilaginous exostoses* so pronounced as to having a deforming effect. Her father, her paternal grandmother, at least 5 of her 8 siblings, and 3 of her 4 living children have the same affection The disease varies considerably in intensity, but in some family members it is so disabling that the patients receive disablement benefit. The patient has born 4 children who are still alive and 2 who died shortly after birth In addition, she has had 4 spontaneous

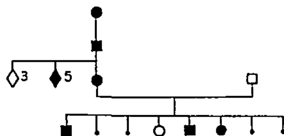


FIG 99 —Multiple cartilaginous exostosis Instance 15

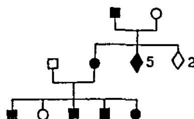


FIG 100 —Ichthyosis vulgaris Instance 16

and 2 induced abortions The past 3 years the patient has been suffering from pernicious anaemia Her husband is normal and of a healthy family She now desires both induced abortion and sterilisation, as she does not think she can prevent another pregnancy There seems to be indication for both operations

A great variety of genetic-hygienic problems may arise in connection with a number of medical and surgical diseases, as well as certain skin diseases and children's diseases. Two instances are given before

16 A woman, aged 28, suffers from *ichthyosis vulgaris* The same applies to 5 of her 7 siblings and 2 more distant relations Her husband is normal and of a healthy family She has borne 5 children, of whom 4 suffer from pronounced ichthyosis v Some of them have had long stays in hospital on account of their disease, which has been complicated by eczema and pityriasis and has caused great suffering The home of the married couple, situated in a fairly remote place in the country, is very poor The possibilities of consistent cleanliness and of having the children under regular treatment are small and complications therefore unavoidable The patient is now pregnant again and desires induced abortion for eugenic reasons The disease is dominant and her request is complied with owing to the bad conditions of treatment in the home Sterilisation is also indicated, if she herself wants it

17. A married woman, aged 38, has 2 children, both boys, 13 and 15 years old, who have had diabetes mellitus since the age of 7 and 2½ years respectively The patient herself is normal, but her maternal grandmother died of diabetes, which had come on at the age of 50, and one or two of her siblings had died young of diabetes Her husband, aged 42, is likewise normal, but his mother died of diabetes The woman is now pregnant again and there is probably about 25 per cent chance that the expected child will have diabetes mellitus If one or both conjugal partners later develop diabetes, the morbid risk for the expected child will increase further *Hence there is*

Genetic hygiene, in the form it has assumed in the Scandinavian countries during the past few decades, must be regarded as a precursor, or perhaps rather as a first stage of this development.

Genetic hygiene is here based on the principle of voluntariness, and the population has learned to understand its purpose. Democratic social conditions prevent misuse and secure that due consideration is paid to personal liberty.

The high standard of the public health service and social care at the same time constitute a basis for genetic-hygienic measures and are necessary for their effectuation.

Medical genetics in connection with the associated advice and registration create the necessary scientific foundation for carrying out measures aimed at preventing hereditary diseases

lesions in the population. For one thing, new hereditary diseases arise through mutation; and, furthermore, it would be impracticable to track down all recessive tendencies. Finally, many dominant affections show varying manifestation and cannot always be detected in the carriers; or a hereditary diseases may in one generation appear in such a mild form that sterilisation is only barely warranted, while in the next generation it may assume a more serious character. A hereditary disease may also not manifest itself till after the patient has had several children, who may very well have inherited the disease. And quite naturally many practical conditions and human considerations may in various ways interfere with a consistent and radical effectuation of genetic-hygienic measures.

Mutations lethal in a homozygous condition may increase viability when they occur in single dose. It has been said that "great wit is to madness near allied"

Some observations indicate that gifted children are not only gifted in intelligence but also in character especially in honesty and truthfulness There are, however, numerous exceptions to this general rule with respect to character, personality and emotional stability. According to some writers sterilisation might readily cut off from the race some of its most valued and versatile members Many valuable members of society, worth more to it than the cost of maintenance of all state institutions put together, would have been lost, if sterilisation laws had been enacted on a compulsory basis a few centuries ago As examples of such members Ludwig van Beethoven, Hans Christian Andersen, Napoleon Bonaparte (!), Michelangelo, Leo Tolstoy and many others have been mentioned

To how great an extent does genetic hygiene ward off disease? To judge from theoretical calculations, this negative selection, which can be effected by moderate genetic-hygienic measures, may probably cause a considerable fall in the incidence of the hereditary diseases in the population This incidence depends, however, on so many different factors that the stated calculations are of limited value.

A definite opinion on the genetic-hygienic possibilities can only be formed on the basis of an empirical material Procuring of such a material requires a genetic-hygienic registration carried through for several generations. We can thereby ascertain whether the hereditary diseases decrease or increase in frequency, and whether the genetic-hygienic measures are employed to a suitable extent and on the diseases where such are needed

During the past 50 years or so the study of heredity, and in particular human genetics, has undergone a development which has added largely to our knowledge of this subject If this development continues the time draws near when man can control his own biological evolution and at the same time to an increasing extent command his environments and conditions of life

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